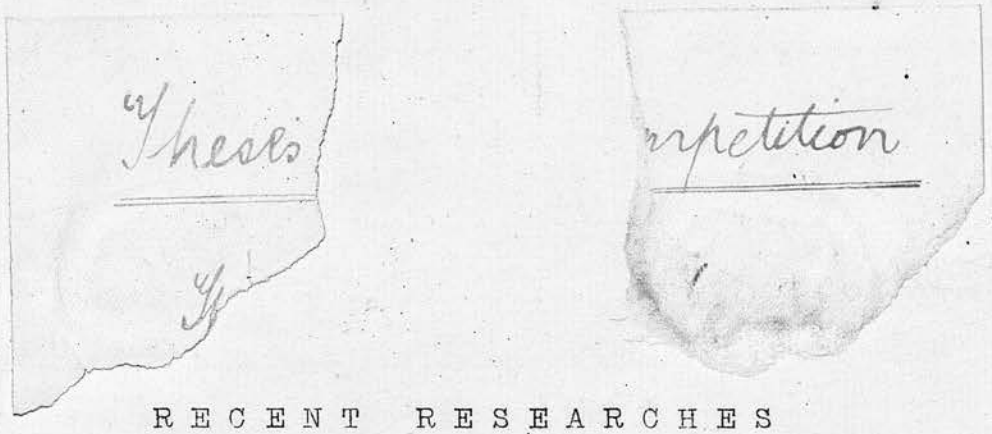

RECENT RESEARCHES

on

LEUCOCYTOSIS,

with

special reference to the so - called

Polynuclear Neutrophile Form.

being a

Thesis submitted to the

University of Edinburgh for the Degree of M. D.

by

John Forbes (M.A.), M. B., C.M., (with

First-class Honours), 1895.

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PORT ELIZABETH,

South Africa,

April 1899.

CONTENTS.

I.

Introductory.

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Two years ago I submitted an essay entitled "The Leucocytosis of Pneumonia" to the Faculty of Medicine of Edinburgh University, which was awarded the Gunning Prize in Peactice of Physic. I was afterwards granted permission by the Faculty to make what use I might of that paper for the purposes of a thesis for the degree of M.D.

Since the date of the handing in of that essay the literature which has been published on the subject of leucocytosis has been immense. Besides many shorter treatises on the subject, the text-books of Cabot (1897) Coles, Türk, and Ehrlich (1898) have appeared, the second one of which is the only one not containing much original and important matter.

The first part of the present thesis treats of the theory of leucocytosis and, with the exception of the short paper read by Muir at the Meeting of the British Medical Association (1898), is the first critical essay of the kind in the English language.

The second part deals chiefly with the leucocytosis of pneumonia as being a typical example of the ordinary polynuclear leucocytosis and largely consists of my Gunning essay re-written and brought up to date. Several statements made in that essay have since received corroboration at the hands of independent observers,

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and some await corroboration. I would note here that the importance I attached to the blood condition found in certain severe cases of pneumonia occurring without a leucocytosis has received additional weight from the fact that about the same time* a similar condition occurring in diphtheria was described by Engel and is an observation which Ehrlich regards as being one of very great moment. I would further point out that the view then taken by me of the relation existing between exudation and leucocytosis is that adopted by Ehrlich in his last work. It will however be noticed that my observations regarding the behaviour of the large mononuclear cells in the ordinary form of leucocytosis is directly opposed to the teaching of that Haematologist.

The third part of the thesis consists of a few general observations and remarks which appear to ~~me~~ me of sufficient importance to merit special mention.

Appended are my detailed observations of the haemic leucocytes in 23 cases of pneumonia ; and a list of the recent text-books and papers bearing on the subject consulted by me.

A large part of the clinical observations which form the basis of this thesis were carried out in the wards of the Royal Infirmary Edinburgh and I have to thank the Professors of Clinical Medicine for affording me every facility in the carrying on of the work. My thanks are also due to Professor Chiene - and

* Engel's first paper appeared a few months prior to the date of my essay, but his work was not brought under my notice until some time after.

and others for like facilities.

I am especially indebted to Professor Greenfield for placing the Pathological Laboratory at my disposal and for many valuable suggestions. I have to acknowledge the courtesy of Professor Ziegler of Freiburg i. Br. for help especially in the literature of the subject.

To Professor Robert Muir who first suggested to me as a subject of research the study of leucocytosis and who was ever ready to direct and counsel me I owe much.

I would also put on record my grateful acknowledgment of the kindness of the late Professor Rutherford who encouraged me to pursue these studies.

I am indebted to Mr Richard Muir for the excellent manner in which he has executed Plates I and II which accompany this thesis.

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PART I.

The Nature of

LEUCOCYTOSIS.

Chapter I.

The Average Number of White Corpuscles in the Circulating Blood.

The discovery of the white corpuscle in the blood of man is credited to Nasse in the year 1835. Since that date these wandering cells of the blood and the closely related cells of the lymph and the fluid of the body cavities have occupied the attention of many able observers in the endeavour to throw more light on their morphological characters, functions, and life history. Of late years much work has been done in connection with, and growing importance attached to, the condition termed leucocytosis in which there is observed an increase of these cells in the blood. In order to give some definite conception as to what ought to be regarded as an increase and what not, it is necessary to consider what is the average number of white corpuscles or leucocytes, as they are termed, occurring in the blood in a state of health.

The number of leucocytes per unit volume of blood is given somewhat differently by the various observers. One cannot be astonished at the differences

set forth if one bears in mind that the numbers thus attained have been arrived at by the employment of methods differing widely in their degree of exactitude quite apart from the amount of care bestowed on the calculation by the several observers. An old and extremely fallacious method, but one recently recommended by Simon, is the so-called "Indirect Method of Enumeration of the White Corpuscles". This method is performed as follows : The red corpuscles are first enumerated by the Thoma-Zeiss apparatus, thereafter on the stained film the relative proportion of the white to the red cells is made out, and then by an arithmetical calculation the desired result is attained. Such a method of enumeration, apparently so simple, is calculated to give very erroneous results. If the films are made in the usual way, i.e.by allowing a drop of blood to spread out between two cover glasses, and then drawing them apart, it will usually be found that the white cells are distributed in relation to the red cells in widely different proportions on the two cover glasses; in other words, as a rule a proportionately greater number of leucocytes adhere to the one cover glass than to the other. A method which can after a little practice be relied on with some guarantee of, at least, a fair degree of accuracy is that in which the leucocytes are counted after moderate dilution of the blood with appropriate fluid, as by

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the method of Thoma-Zeiss. If the operation is performed with care and the leucocytes counted over a sufficiently large cubic area of the diluted blood the results arrived at may be regarded as tolerably accurate. (See p. 81.)

It must however be recollected that the distribution of white corpuscles in the blood stream of the peripheral vessels is not constant, but is liable to be influenced by vaso-motor phenomena, etc. The number of leucocytes also varies to some extent with the nature of the vessel under observation, whether artery, capillary, or vein. It should therefore be the duty of the observer in studying the comparative variation of those cells occurring from hour to hour or from day to day in the general circulation to take at each observation as nearly as possible similar blood; therefore in experimental work on animals the blood from, if possible, the same vessel should be examined, and in clinical work the blood should be taken preferably from the lobule of the ear. The variation from the causes however, may be regarded as trifling and the experiment of Stiénon who seeks to demonstrate great differences in the number of the leucocytes in the blood taken simultaneously from different fingers of the same individual only serves to throw doubt on the accuracy of his technique, notwithstanding the assertion that it was carried out "with all necessary precautions".

The influence of digestion on the number of the white blood corpuscles must also be borne in mind. I shall afterwards refer more particularly to the Digestive Leucocytosis, as the increase of leucocytes occurring in the blood of the general circulation in connection with this process has been termed.

The average count of the total number of leucocytes per cubic millimetre of blood of the healthy individual varies as follows, according to some of the best known and more recent authorities on Leucocytosis :-

	Lowest			Highest.
Thoma and Lyon	6784	-	-	10590
" "	4430	-	-	7066
Tumas	4800	-	-	9600
Halla and Boeckmann	4960	-	-	10106
Graeber and Reinecke	7134	-	-	7351
Rieder	4200	-	-	9600
v. Jaksch	7107	-	-	7482

Two series of observations.

Rieder gives the average for 20 healthy adults, who had fasted for 18 hours, as 7680, and for 12 children who had fasted for 12 hours, as 9660.

Osler lays down the normal as 6000

According to the observations of von Limbeck the normal count for the fairly well nourished individual, who is neither at the height of digestion nor has long fasted, varies between 8000 - 9000 leucocytes per c.m.m., but a difference of 1000 on either side of these numbers he regards as being still within the normal limits.

The last named author also lays importance upon another factor which must be taken into consideration in estimating whether in any particular case one is dealing with an excess, a diminution, or a normal number of leucocytes, and that is, the nourishment of the patient. "In general" v. Limbeck proceeds to say "well nourished individuals show a higher average leucocyte count in the blood than ~~a~~ specially reduced individuals even though these are 'healthy'. This fact appears to me of a certain practical importance and one which should always be taken into consideration according to my opinion in the determination of the absolute leucocyte count in the blood of patients. The basis number, anything exceeding which to be regarded as evidencing a pathological leucocytosis, is not always the same. So, for instance, in the case of a robust man the

-absolute

absolute count of 10000 leucocytes per c.m.m. cannot be deemed excessive, while for a reduced individual a like count must on the other hand be regarded as indicating a pathological increase".

Chapter II

The Various Classifications of the Varieties of Leucocytes.

Further, as in Leucocytosis there is not only to be observed an increase in the total number of Haemic leucocytes but also a disturbance in the relative proportions of the different varities to each other it isnext necessary to briefly note the various forms of these cells found in the circulating blood along with the various classifications proposed by different observers.

It was Wharton Jones who in the year 1846 first discovered that the white cells of the blood and lymph were not all of one kind. He divided them into "granular" and"nucleated" cells. His observations together with those of Rindfleisch in 1863 were confirmed, a year or two later by Max Schultze who further differentiated the white cells of the blood into the following four groups :-

1. Small round cells with round nucleus and little clear protoplasm.
2. Larger cells with round nucleus and more clear protoplasm.
3. Cells with finely granular protoplasm and one, two or more nuclei.

4. Cells with coarse granules in the protoplasm.

Ehrlich in 1878 and following years more particularly examined by means of aniline dyes the granules of the corpuscles and classified them according to their relative affinity for basic, acid, or neutral dyes. He made out the existence of five forms of granulation associated with as many varieties of wandering cells. His table of cells according to their granules is :-

α - Granulation. - Eosinophilic, present only in small numbers in human blood; granules coarse, stain readily with acid dyes.

β - granulation. - Amphophilic, cells frequent in rabbits and guinea-pigs in blood; present in man in medulla of bones; stain both with acid and basic dyes; granules fine.

γ - granulation.- Large cells found in connective tissue; "Mastzellen", in blood of man only in certain cases of leukaemia ; stain only with basic dyes; granules coarse.

δ - granulation. - Fine basophilic, mostly "mononuclear"; stain with basic dyes.

ε - granulation. - Neutrophilic. The most frequent leucocyte of human blood; polynuclear; stain only with neutral dyes.

-Metchnikoff

Metchnikoff, basing his classifications on the action of the different cells towards microbic and other foreign particles introduced into the organism, distinguishes the following forms :-

1. Lymphocytes = immature leucocytes.
2. Large hyaline cells, mononuclear, phagocytic, "macrophages".
3. Smaller neutrophile cells, polynuclear, "microphages".
4. Eosinophilic cells - not phagocytic.

Kanthack and Hardy in 1893 showed that neutrophile and amphophile cells did not exist as such, the so called neutrophilic and amphophilic granules in reality being faintly oxyphilic, or, in other words having a feeble affinity for acid stains.

Other classifications have been proposed by Löwit, Hayem, Bizzozero, Heyl, Renaut, and Uskow, but those given above are generally regarded as types and have been recently admirably collated in tabular form by Adami. (Table 1. see next page)

Table 1.

Collation of the different Classifications of the Varieties of Leucocytes. (Adami).

Kanthack & Hardy	Ehrlich	Metschnikoff	Max Shultze	Wharton Jones
mphocyte	Lymphocyte	Lymphocyte	Small round cell I.	non-granular
aline Cell		Macrophagocyte	Large round cell II	nucleated cells
arsely granular yphile cell	Eosinophile cell	Eosinophile cell	Cells with coarsely granular protoplasm	Granule cells coarsely granular
nely granular oxyphile cell	Neutrophile Amphophile	Microphag - ocyte	Cells with finely granular protoplasm	Granule cells finely granular
arsely granular basophile cell	Basophile cell with granulation			
nely granular basophile cell	Basophile cell with granulation		Cells with finely granular protoplasm	Granule cells finely granular

Chapter III

Normal Histology of the white Blood Corpuscles.

I shall now give a brief description of the different varieties of haemic leucocytes found normally in man. In the following account of the lymphocytes and large moronuclear cells I draw largely from the description given by Ehrlich in his recent work on Anaemia. (1898)

-1. Lymphocytes

1. 1. LYMPHOCYTES. (Syn. ~~Sign~~ - small mononuclear leucocytes.) See Plate II Fig. 1. 2. 3 a.

These are small cells, as a rule about the size of red blood corpuscles, spherical in shape, possessing a relatively large, deeply staining, centrally placed, spherical nucleus, and little cell substance. Nucleus and protoplasm are basophile; indeed by many methods of staining the protoplasm shows a far greater affinity for the basic dyes than the nucleus; the nucleus then appears as a relatively fainter area in the peculiarly retieulated, intensely stained protoplasm. One notes frequently within the nucleus one or two nucleoli with a relatively thick, deeply stained menbrane. The protoplasm shows with methylene blue and kindred stains ~~are~~ an unequally intense coloration, which, Ehrlich remarks, is not, as he first understood it, the expression of granulation, but rather must be regarded as that of a reticulated structure. Further the contour of the lymphocytes, at least in the larger forms, generally is not quite smooth, but somewhat teased out, scolloped, ragged often, and especially so in the very large forms, parts of the principal portion may become detached, and be found present in the circulating blood as small free plasma elements. In stained preparations, especially in lymphatic leukaemia, these are easily recognisable in their character and origin through their staining, -which

which fully corresponds with the staining of the protoplasm of leucocytes. As regards the further metamorphosis of the nucleus, one finds - generally fairly seldom - a sharp incurvation of the nucleus upon itself." It appears clear from the accompanying diagram (Fig.3. l.c. p. 47 after Rieder's atlas.) that in this case altogether different nuclear forms are present, than those which are characteristic for the polynuclear elements."

"For acid and neutral stains the protoplasm shows no special affinity."

"Generally as above stated, these cells are distinguished in the blood of the healthy adult by their small size, which comes near to that of the red blood corpuscles. On the other hand one finds in the blood of children under normal conditions larger forms, and in lymphatic leukaemia especially large forms, which have often been misinterpreted by inexperienced observers."

"One-sided increase of the lymphocytes occurs, but in comparison to the other forms is much rarer and has been appropriately designated by the special name "Lymphocytosis" or "Lymphaemia".

2. LARGE MONONUCLEAR LEUCOCYTES. - (Syn. Hyaline Leucocytes). See Fig 1.2 c. Plate II

These are strictly to be differentiated from the first group. They are large cells of about

-two

two to three times the size of erythrocytes, which have one large oval, mostly excentrically placed and weakly staining nucleus, surrounding which is a relatively large amount of protoplasm. The latter is free from granulations, faintly basophilic, and indeed in contradistinction to the protoplasm of lymphocytes, stains more fully than the nucleus. Their separation from the lymphocytes is grounded upon the circumstance that they differ from this type in their whole morphological character, and transition forms between the two are not observed. The origin of these cells, whether from the spleen or bone morrow is uncertain.

These large mononuclear leucocytes undergo development in the blood into :-

3. THE TRANSITIONAL FORMS.

These differ from the foregoing by the nucleus becoming indented and taking on more or less of a reniform shape, further by a greater ~~activity~~ affinity of the nucleus for the nuclear stains, as also through the appearance of scanty neutrophilic granulation in the protoplasm.

The term "Hyaline" applied to the large mononuclear and transitional leucocytes is, as Durham remarks, a particularly unhappy one.

4. THE "POLYNUCLEAR " LEUCOCYTES.

~~Sign~~ Syn. - They are also referred to, more correctly, as polymorphous leucocytes. Kanthack

Kanthack and Hardy term them "finely granular oxyphilic")

They are somewhat smaller (Plate II Fig 1.2.3 6.) than either groups two or three. The nucleus is an exceedingly irregular structure branching thoughtout the cell, The lobes are usually united by fine bands of Chromatin, so that the nuclear figure takes S, Y, E, Z, forms. The irregularity is undoubtedly, as Arnold first suggested a sign of the amoeboid activity of the cell; this fact has since been corroborated by Haidenhain, Metchnikoff, and others.

The nucleus stains deeply with all nuclear stains. The cell body is finely granular; these granules stain feebly with eosin and other acid dyes. Durham says that in specimens made from the human subject shortly before death, the granules do not appear. Hankin considers he has noted a loss of granulation in these cells in the presence of microbes etc., and he supposes the granules are the source of the alexins or natural bactericidal substances. Hahn, Durham, and others assert they have never observed the process in their investigations. Janowski has lately found all stages from rarefaction to total disappearance of the neutrophile granulation in purulent form. I have never noted loss of granulation in these cells in the blood in cases of croupous pneumonia or in other acute inflammatory conditions.

-These

These cells form by far the greater proportion of the cells found in acute inflammatory exudations and constitute the overwhelming majority of all the cells found in the consolidated lung of croupous pneumonia. Here, however, owing to degenerative changes, they are frequently only with difficulty recognised.

I have moreover observed them in great numbers in the sputum of patients suffering from croupous pneumonia. At an early stage of the affection, when the microscope may reveal the cellular elements of the expectoration as being made up almost entirely of these cells, <u>their recognition therein is a matter of considerable diagnostic importance</u>.

EOSINOPHILIC LEUCOCYTES. -

These cells are also known as the coarsely granular oxyphilic cell. In man this cell is larger than the polynuclear cell. The nucleus is horse-shoe-shaped or lobed; in the latter case the lobation is usually not so marked as in the case of the typical polynuclear cell (Plate II figure 3 e) A nuclear network may generally be made out. The cell granules are relatively large, spherical, or slightly ovoid bodies and have a strong affinity for acid dyes. Recent micro-chemical tests have demonstrated that the granulation is albuminoid in nature and, as it is of

-stable

stable composition, resists decomposition and is not digested in the gastric juice, Weiss places it among the nucleo-albumins and proteids. As regards the province of the eosinophilic granules there exist various views, Hankin and Kanthack promulgated the theory that these granules produced alexins. Siawcillo as the result of his observations cannot confirm this hypothesis; nor has he been able to see any change either in quantity or in the form of the granules of these cells found in the exudate provoked by the injection of bacteria. Neither can Durham find that it plays a prime part in the tissue-battle against micro-organisms nor can he trace any indubitable or apparent loss of granulation as a result of contact with bacteria. Sherrington also has noted the high resisting power of the coarsely granular leucocyte to various chemical agents.

Ehrlich believes that in general the granules of the wandering cells are destined to be given up to their surroundings. This elimination, he concludes, is perhaps one of the most important functions of the polynuclear leucocytes.

Apart from the blood eosinophilic cells are also present in numbers in bone marrow, in the coelomic fluids, and in the lymph spaces throughout the body. In different situations however they exhibit -certain

certain differences in form and character. (Muir, Kanthack and Hardy, Hardy and Wesbrook).

6. "MASTZELLEN". -

These are, according to Ehrlich present although in very scanty numbers, in every normal blood; they ought not to exceed 0.5 % in number.

In them there is an intense basophilic granulation of very unequal size and distribution. In triacid preparations the granulation is unstained, and the mast cells appear in these as clear, polynuclear, granulation-free cells.

— the most important just described by Ehrlich and Lazarus

Chapter IV

The relative proportions of the Different Forms of Haemic Leucocytes.

On the next page in tabular form are given the percentage ratios which the different varieties of haemic leucocytes bear to each other in man in a condition of health according to the opinions of the various observers enumerated. (Table II)

It will be noted from a survey of the figures given there that the relative proportion of the different forms to one another is not a fixed one: normally it is subject to considerable variation in the case of different individuals and also varies to some extent in the same individual at different times. Notwithstanding this the fixity of the proportional relation is sufficiently constant to enable the observer in the great majority of cases to determine whether in a particular case the ratio which is present is one which may be considered as occurring within physiological limits, or, on the other hand, is one which indicates the intervention of a pathological process. I believe that the intelligent observation of the changes occurring in the relative proportion of these cells and even more so the changes in their absolute number per unit volume of blood will in the

TABLE II

	Lymphocytes.	Large Mono. & Transit.	Polyn.	Eosinoph.
EHRLICH	22. 25	2 . 4	70 . 72	2 . 4
CABOT	20 . 30	4 . 8	62 . 70	½ . 4
HAYEM	23		70	7
USKOW	18		75	6
STIENON	20 . 30		60 . 75	1 . 5
KANTHACK & HARDY	-		75 . 90	2 . 4
v. LIMBECK			70 . 80	2 . 8
RIEDER	24 . 33		-	-
GRAEBER	15 . 35(av.24)			
LÖWIT	20 . 3		79 . 7	

future be fraught with no unimportant results.

Lymphocytes. - These and the large mononuclear are considered together by many authors in this connection. This is a mistake, and I attach much importance to the comparison of the reciprocal relation of these cells.

The percentage in the blood of the general circulation of the small mononuclear leucocytes is from 20 - 30 % of all the wandering cells. They are said to be increased during the process of digestion. (Okintschitz, Kanthack and Hardy.)

Large mononuclear. - Under this head are included the so-called transitional cells. Simon computes the count of the large mononuclear and transitional cells as together totalling 6%. Graeber estimates as 5 - 10% eosinophili and transitional cells together. I think, we may with near approach to accuracy say, that the large mononuclear and transitional cells represent in the circulating blood from 2 - 6% of all leucocytes present.

Polynuclear. - These cells are present in the blood of the healthy adult in the proportion of 60 - 75% of all the haemic leucocytes.

The percentage ratio of the polynuclear cells is greatly increased in the most common form of leucocytosis.

-Eosinophilic

EOSINOPHILIC. - The following are further observations on the average number of these corpuscles in the blood :-

Ehrlich 2 - 4%. Gabritschewsky 1-2-3%

Canon 1-- 3% Zappert 0 . 67 - 11%

Muller & Rieder 1 - 4%

ZAPPERT, whose work on Eosinophilic cells is regarded as the standard, says that on the average these cells vary in health from 50 - 250 in the cubic millimetre, but that in apparently quite healthy individuals unexplained increase of the oxyphile cells in the blood can be observed, so that these may number as many as 700 per c.m.m.

We may conclude : Eosinophilic cells are present in the blood to the number of from 1 - 6% of the total number of leucocytes.

In the blood of children according to Rieder, Canon, Zappert, they are present in a considerably higher proportion. Their absolute number is greatly increased in the blood in leukaemia. The expectoration of asthmatics is chiefly made up of these cells. Among other conditions they are undoubtedly greatly increased in certain cases of anaemia, skin diseases etc.

Chapter V

Pathological Forms of the White Blood Corpuscles.

In pathological conditions cells are found circulating which are not present in normal blood. These I shall shortly describe.

1. Mononuclear cells with neutrophile (finely granular oxyphilic) granulation. ("Myelocytes", Ehrlich).

These are for the most part large cells, with a relatively large, faintly staining nucleus, usually fairly centrally situated in the cell. In contradistinction to the large mononuclear leucocyte of normal blood the protoplasm shows fine granulation of a neutrophile character. Besides the large forms one meets with much smaller varieties approximating the size of red blood corpuscles; all transitions between these two sizes of corpuscles are also met with.

In contradistinction to the polynuclear neutrophilic (finely granular oxyphilic) leucocytes these mononuclear cells show no amoeboid movement on the warm stage. They are found regularly and characteristically in myelogenous leukaemia, and are very numerous in this disease. They have been described as present in many other affections, more especially in pernicious

pernicious anaemia, in anaemia pseudoleukaemica infantum, and in other severe anaemias. (Cabot, A. Lazarus, Neusser, Engel, Klein etc.).

Of a special interest, says Ehrlich, is the appearance of Myelocytes in infectious diseases. Rieder had demonstrated that in acute infectious diseases Myelocytes may appear, and C. S. Engel in a late work has gone fully into the phenomenon of their appearance in diphtheria. "Engel found", Ehrlich goes on to say, "the interesting fact, that in children suffering from diphtheria myelocytes were often demonstrable in the blood, and further made the important observation that a high myelocyte count (3 . 6 - 16 . 4% of white cells) is only found in severe cases, and indicates an unfavourable prognosis. In light cases myelocytes likewise appear, but not regularly and in much fewer numbers".

Engel's statement regarding the occurrence of a high percentage of myelocytes in certain unfavourable cases of diphtheria, ~~are~~ is in entire concord with the results of my own observations in croupous pneumonia, which are to be found recorded in my Gunning Essay on the "Leucocytosis of Pneumonia" handed in to the University of Edinburgh in March 1897, the same year as that in which Engel made known the results of his observations in diphtheria. I shall refer more particularly to the occurrence of these cells in pneumonia in treating of the leucocytosis of that disease.

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2. Mononuclear eosinophile cells. (" eosinophile Myelocytes"). These are the eosinophile analogue of the preceding group, and are much larger than the polynuclear eosinophiles; smaller varieties also occur. Eosinophile myelocytes occur almost regularly in myelogenous leukaemia and in anaemia pseudoleukaemica infantum.

3. Small neutrophile Pseudo-Lymphocytes.- These are about as large as the small lymphocytes, possess a round, intensely coloured nucleus, and a narrow zone of protoplasm showing neutrophile granulation. The relatively intense coloration of the nucleus and the small proportion of protoplasm to the cell is sufficient for a differentiation from the small forms of myelocytes which usually are not found of so small a size. They are division products of the polynuclear cells. (Ehrlich). They are rarely found in the blood; are also present in fresh pleuritic exudations.

4. "Irritation forms". ("Reizungs formen"). These have been quite recently described by Türk. They are non-granular cells with one nucleus. They possess a protoplasm which stains of an intense deep brown colour with the triacid solution, and, further, a simple round, often eccentrically placed nucleus, which stains of a deep blue green colour, but which shows no clear chromatin stroma. The small forms vary between lymphocytes and large mononuclear leuco-

cytes; they approach for the most part in size and general character to the first named. According to Türk's researches these cells occur often in company with and under the same conditions as myelocytes.

Chapter VI

The Place of origin and the Relation of the different varieties of Leucocytes to each other.

Erb believed that the lymphocytes develop into large mononuclear, and that these by multiple partition of the nucleus become resolved into polynuclear cells. Virchow in his later treatises expressed similar views.

Löwit has demonstrated that the blood in veins returning from bone marrow, the blood in the portal vein and in the vena cava superior below the entrance of the thoracic dust shows a considerable preponderance of mononucleated over polynucleated white blood cells; also by simple pressure on the abdomen Löwit was able to cause an important increase of the mononucleated cells in the circulating blood. The different size of the white blood cells, whose origin is especially in the spleen and the lymph glands, is according to Löwit, alone conditioned by progressive development from the small and young to the large and old forms. The nuclear metamorphosis which occurs in the development of the mononucleated into the polynucleated form, he regards as a degenerative change.

- Max Shultze

Max Shultze believed that the lymphocytes orignate from the bone - marrow, spleen, or lymph glands, and thus enter the blood - stream; there they develop into the large mononuclear and further into the polynuclear cells. Lastly through the development of of large granules in the cell the polynucleated corpuscles mature into coarsely granular (eosinophilic) cells. Schultze says he has observed transition stages between the finely and coarsely granular corpuscles.

Erlich was formerly of the opinion that the blood forming organs furnish to the blood only mononuclear leucocytes. He regarded the different kinds as successive stages of development from the lymphocyte to the eosinophile. H. F. Muller accepts this view and like M. Schultze declared he had observed transition forms from the neutrophile to the eosinophile granulation.

Maragliano, and Zappert also believe the eosinophile cells are the further developmental stages of lymphocytes, the latter declaring that all the eosinophile cells have passed through the stage of the neutrophile.

Rieder regards the change of configuration of the nucleus as being associated with increased amoeboid movement and augmented power of emigration. Arnold, Haidenhaim, Metchnikoff are of like opinion. The last named further quotes the Russian observer Uskow, who also looks upon the polynuclear cells as

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a further development of the mononuclear. Sherrington remarks that by general agreement the polynuclear leucocyte is regarded as par excellence the leucocyte of exudation, and believes that the nucleus of the corpuscle in repose resumes the spherical form.

Gulland believes that all leucocytes are derived from the lymphocyte.

Marquévitch (1895) claims he has demonstrated experimentally the transition of the mononuclear with the polynuclear corpuscle, and that the development is hastened by different agencies, such as for instance, the inhalation of oxygen, the introduction of tuberculin into the blood, etc.

On the other hand Kanthack and Hardy believe that the large mononuclear is developed from the small mononuclear, but that further development into the polymorphous corpuscle takes place, these authors do not admit; while Buchanan in a recent article on Leukaemia believes that the different forms of cells are distinct and separate varieties.

This much vexed question has reached another stage during the past year by the publication of Ehrlich's views, the outcome of careful experimental observation by himself and others and the consideration of clinical facts.

As the result of such experimental work which is fully detailed in his work Ehrlich comes

-firstly

firstly to the conclusion that "the importance of the spleen for the production of the white blood corpuscles can in no way be considerable, and that if indeed cells are produced by it, these must be non-granular. The spleen stands indeed in its function in less close relationship to the lymph gland system, than to the bone marrow. Assuredly the spleen has not the slightest relationship to the common leucocytosis."

Secondly, As regards the lymph glands, he points out that in certain enlargements of these, e.g. malignant lymphoma, a lymphocytosis is to be found in the blood. He explains the lymphocytosis which occurs after extirpation of the spleen, by referring such increase to vicarious enlargement of these glands. He refers to Rieder's experiment on digestive leucocytosis, which went to show slight proportional increase of the lymphocytosis; also to the lymphocytosis which Weiss found in gastric and intestinal catarrh. Ehrlich comes to the conclusion, that a lymphocytosis occurs if in more or less extensive lymph gland districts an increased lymph circulation takes place, and more or less lymph elements are mechanically washed out of the glands as a result of the increased flow of lymph through these glands. Further, as compared with the multitude of chemical substances which when injected cause a leucocytosis, only one- pilocar-
-pin

pin - has been known to produce a lymphocytosis, a substance which secondarily causes an increased flow of fluid containing lymph cells into the blood. As illustrating the want of contractility of the lymphocytes he refers to the experiments of E. Newmann. This observer caused pusformation in a patient with lymphatic leukaemia, whose blood contained only a trifling number of polynuclear cells. The examination of the pus showed, that it was exclusively composed of polynuclear cells and that not a single lymphocyte which were present in the blood in such numbers was met with in the exudate.

Thirdly, Ehrlich deals with the relation of the bone marrow to the formation of leucocytes.

He notes firstly that in man,, as also in a great number of animals (e.g. Apes, Guinea-pigs, Pigeons) the bone marrow shows the peculiarity, that the cells produced by it are the bearers of a specific granulation, in sharp contradistinction to the lymph gland system which in the whole animal series carries granulation free cells.

The first group of bone marrow cells are those containing fine granules; in the man and ape the granulation is neutrophile. These cells compose the great majority of all the bone marrow cells.

The second group of bone marrow cells carry
-granules

granules which are to be found in all vertebrate animals from the frog to man. These are (1) eosinophilic cells, and (2) basophile mastzellen.

The granulation free structure of the bone marrow show mostly mononuclear cells of different type. They take a place both as regards number and importance far behind the granular cells particularly the prevailing first group.

If one examines a stained dry preparation of the bone marrow, for instance of guinea-pigs, rabbits, man etc. one sees that the characteristic finely granular cells are present in all stages of the development from the mononuclear, through the transition forms, to the polynuclear, as we meet them also in the circulating blood. A glance at such a preparation demonstrates, that the bone marrow is clearly the place of formation, where continually out of granular mononuclear cells the typical polynuclear cells are formed.

"The same kind of development can be here also seen for the polynuclear eosinophilic cells ...

"Of the cells with specific granulation present in the bone marrow we find only the developed forms in normal blood while the mononuclear and the transitional forms of the neutrophile group do not pass over into the blood stream under normal conditions.....

"Ifwe consider then, that only in the bone

-marrow

marrow polynuclear neutrophile cells are developed and stored up, that in common leucocytosis, there is a one-sided increase of the polynuclear forms alone in the blood stream, the conclusion is clearly to be drawn therefrom, that leucocytosis is a pure function of the bone marrow....

"Again we might further draw special attention to the fact that the large mononuclear and the transitional forms of normal blood do not participate in the increase in common leucocytosis; in a leucocytosis of high degree their percentage ratio can be even reduced, due to the one-sided increase of the polynuclear cells, It appears therefore that these elements do not respond to characteristic stimuli, and probably chiefly arrive in the blood in another way than the polynuclear.....

" As to the place of formation of the non-granular large mononuclear leucocytes one cannot speak as yet with any certainty."

Ehrlich thereafter adduces certain pathological conditions, e.g. acute leukaemia, where, according to him, the blood condition present would corroborate his theory as to the place of formation of the polynuclear cells being for the most part in the bone marrow.

R. Muir in a paper read at the British Medical Association (1898) showed that the finely granular marrow cells undergo great proliferation -in cases

in cases of long continued leucocytosis, and came to the opinion quite independently of Ehrlich, that the bone marrow is the site of the formation of these cells.

That the lymphocytes of the blood owe their origin to the lymph glands, that the finely granular neutrophile (oxyphilic) leucocytes are produced in the bone marrow, and that these two varieties of cells are, as regards their origin, quite independent of each other, there now appears to me no reasonable cause for doubt.

Ehrlich's statement regarding the behaviour of the large mononuclear cells in ordinary leucocytosis I shall criticise later.

Chapter VII

The Different Forms of Leucocytosis.

A marked increase in the number of white corpuscles in the circulating blood occurs in several conditions which nevertheless widely differ as regards their pathological basis.

Virchow understood by leucocytosis the condition of increase of the colourless corpuscles of the blood, which appears to be dependent on irritation of the blood forming glands, especially the lymph glands.

Pée in his treatise on Leucocytosis (1890) thus expresses himself :- By Leucocytosis one understands a transitory and generally a slighter increase of the white blood cells than is the case in Leukaemia. Among others, Eichorst, v. Jaksch, Jurgensen, Seifert and Müller, Strümpell, O. Vierordt, Gowers and Taylor, and Hamilton hold similar views.

A more precise rule for distinguishing between these two conditions was laid down by M. Huss who declared that where the proportion of the white to the red corpuscles reached one to twenty, then the case of one of Leukaemia. Later the line of demarcation between leucocytosis and leukaemia was given -as one

as one to fifty.

The inaccuracy of this rule was soon demonstrated by various observers. Cases of leucocytosis were reported, especially in anaemic individuals, where the relative number of white corpuscles attained to or even surpassed the high figure.

With the advent of the new staining methods it was observed that in the vast majority of cases marked qualitative differences between the two conditions were demonstrable in the blood. As a general rule it was found that in leukaemia there are to be observed cellular elements not present in healthy blood, while in leucocytosis the increase is due to augmentation in number of the white cells normally found in the blood, and usually, although not universally, to a specially large increase of the polynucleated (finely granular oxyphilic) forms relatively to the other leucocytes in the blood. This important point is recognised by Eberth in his definition of leucocytosis :-

By leucocytosis is understood a disproportional increase of the polynuclear leucocytes or such (white) elements as normally are present in healthy blood."

The definitions given by Rieder, v. Limbeck, and Cabot closely correspond with that of Eberth.

Ehrlich, who had specially in view the differentiation of the common form of leucocytosis from "spleno-medullary" leukaemia, regarded as pathognomonic of the latter affection an increase of eosinophilic -cells

cells, which he declared were always present in excess - sometimes to a high degree - in that disease. Ehrlich's assertion was however misunderstood by many observers including v. Limbeck, who thought that he referred to a relative excess of these cells over the other varieties and it was pointed out that the eosinophilic cells were not always relatively increased in leukaemia. Ehrlich had however spoken of the absolute increase of the eosinophilic cells, and he has since maintained that such an increase is always to be found present in cases of leukaemia.

The diagnostic sign which later emanated from H. F. Müller-- the occurrence in the blood of Cornil's Markzellen - is if taken by itself found to be unreliable for the diagnosis of leukaemia.

Leucocytosis is not however constantly attended by an excess of polynuclear cells.

On the other hand according to most observers the leucocytosis of new born infants is associated with a proportional increase of mononuclear cells. But not so infrequently also in the pathological forms no special preponderance of the polynuclear cells is to be met with; while in other cases the mononuclear cells are proportionally to the other greatly increased.

This leads us next to consider shortly the different forms of leucocytosis. Ehrlich, who em-
-braces

braces under the term leucocytosis any increase in the number of white corpuscles in the blood, divides (1898) all forms of leucocytosis into two great classes, active & passive leucocytosis. Under the head of active leucocytosis are included those forms of leucocytosis in which those cells are increased which as the result of chemotactic stimuli actively migrate into the blood stream. Under the passive leucocytosis are included those cases in which the count of the cells ~~are~~ is increased which have no power of movement of their own, but which are washed into the blood stream as the result of mechanical forces.

Passive leucocytosis is exemplified by the different forms of lymphaemia, which is to be found not only in the course of different diseases, but also in the increase of lymphocytes occurring in leukaemia.

The active forms of leucocytosis are divided into the following sub-divisions :-

(a) Polynuclear leucocytosis.

1. Polynuclear neutrophile leucocytosis.
2. Polynuclear eosinophile leucocytosis.

(b) Mixed leucocytosis with the participation of granular mononuclear elements: "Myelaemia."

(a) 1. Polynuclear Neutrophile Leucocytosis.

This is the most common variety of the different forms of leucocytosis.

In this form the percentage rates of the polynuclear forms is increased and often to a great

-extent

extent so that these corpuscles may come to number as many as 90 % or more of the total number of leucocytes. The percentage rates of the lymphocytes is reduced, sometimes even as low as 2 %, but their absolute count may not be reduced, Often however the absolute count of these corpuscles per c.m.m. of the circulating blood is greatly below normal, as Ehrlich pointed out in one case, and as may be seen from Türk's or my own observations in inflammatory leucocytosis. In the common polynuclear neutrophile leucocytosis the eosinophile cells are absolutely diminished, sometimes they are absent.

Some of the cases show beside the increase of neutrophile cells, an increase rather than a diminution of the eosinophiles clinically Ehrlich divides the polynuclear neutrophile leucocytosis into :-

A. Physiological Forms of Leucocytosis.

To this section belongs digestive leucocytosis, the leucocytosis occurring after bodily exertions, or after cold baths, also the leucocytosis of pregnancy.

Of the physiological forms the digestive sub-variety need only be referred to here as it might possibly influence clinical observations in cases of inflammatory leucocytosis.

From one to six hours after the principal meal the number of leucocytes circulating in the blood is said to be increased, diminishing soon after to

-normal.

normal. The increase however is not so great as some authors, notably v. Jaksch, would lead one to suppose, and as a rule is only evident when an individual who has previously fasted for some considerable time partakes of a full meal. The increase is said to be due to an excess in the number of lymphocytes or small mononucleated cells and to a less extent of the basophile cells of the blood (Kanthack & Hardy). On the other hand Rieder finds no increase in the percentage of mononucleated cells in digestive leucocytosis but finds a marked diminution of the eosinophilic cells under the same conditions. Sherrington is also of the opinion that fasting increases the number of eosinophilic cells in the blood. Further investigations are required to throw light upon these points.

B. Pathological Forms of Leucocytosis.

1. The increase of the polynuclear cells in infectious processes - the Inflammatory Leucocytosis of most observers. As regards this form of leucocytosis, if Virchow's view were correct one would expect to find the occurrence of a leucocytosis in all diseases attended with irritation of the lymph glands, provided that irritation was not so great as to cause destruction of the gland substance. Therefore in those diseases specially associated with enlargement of the lymph glands, such as typhoid, erysipelas, pneumonia, an abnormal increase of the white corpuscles would occur.

-Halla

Halla refers inflammatory leucocytosis to disease of the whole lymph system especially of the spleen, lymph glands and bone marrow.

Escherich in his sketch on cachectic leucocytosis supports Virchow's view and cites the experimental work of Lassar who found that, through irritation from without, inflamed and swollen lymph glands produced lymph in greater quantity, more concentrated and richer in cell elements.

Next comes the sweeping assertion of Bockman who avers that in acute fevers the count of the red corpuscles varies inversely, and the count of the white corpuscles varies directly, with the height of the temperature.

When however these theories were put to the test by clinical observations, it was found that none of them held good. Acute phthisis, a disease associated with high temperature, showed as a rule a normal number of colourless corpuscles. Typhoid fever, a disease pre-eminently associated with glandular enlargement, was found to run its course without leucocytosis. Further, in those inflammatory conditions associated with increase of white blood cells, a high degree of fever did not necessarily imply a high degree of leucocytosis.

Rieder's explanation of such seeming discrepancies is that the increase of the white blood corpuscles is much less dependent on the temperature than on

-the

the localisation of the process and the entry of certain chemical substances into the blood.

Lastly, comes von Limbeck's assertion that acute diseases attended with fever and exudation (with the exception of those of a tubercular nature) are regularly accompanied by a leucocytosis, while in those infectious diseases associated with no exudation (typhoid, intermittent fever, sepsis) leucocytosis is as regularly absent.

With these points before us it were well briefly to summarise the results of clinical investigations directed towards the computation of the white corpuscles in various acute diseases.

Most observers are agreed that acute non-tubercular inflammation of the serous membranes (pleura, peritoneum, meninges), such as are accompanied by exudation, are generally associated with leucocytosis which reaches a high degree in those cases in which the exudate is purulent. In tubercular inflammation of those membranes on the other hand it is said that leucocytosis is generally absent. A high degree of leucocytosis is found too in all other acute suppurations where the exudate is at all extensive, also in erysipelas, in scarletina, and in osteo-myelitis. In diphtheria the leucocyte count though still high is rather less than in the last named diseases. A moderate increase is observed in most cases of acute articular

-rheumatism

rheumatism during the fibrile period. Authorities are practically unanimous that typhoid fever is attended with no leucocytosis, and if such appear it is due to some complication occurring in the course of the disease. In pulmonary phthisis, acute or chronic, a normal number of white cells is usually observed. Quite recently Stein and Erbmann have stated as the result of a series of observations that leucocytosis occurring in pulmonary tuberculosis is not due to the tubercle bacillus but to a secondary infection leading to breaking down of the substance of the lung - a septic process due to the activity of various virulent bacteria and cocci. A normal number of leucocytes is also as a rule counted in typhus fever, measles, variola, catarrhal bronchitis, and acute nephritis. In malaria, quite apart from the administration of drugs, most observers are agreed that an appreciable diminution of leucocytes takes place in the blood of the general circulation.

2. The Toxic Leucocytosis. - This often occurs in poisoning with the so called blood poisons: e.g. Phenylhydrazin derivatives, Pyrodin, Phenacetin, etc. etc.

3. The Leucocytosis which accompanies acute and chronic anaemic conditions, Especially post-haemorrhagic anaemia.

4. The Cachectic Leucocytosis, in malignant

-tumours

tumours etc.

(Note :- The Agonyal or Pre-mortal Leucocytosis first described by Litten probably does not occur as such but as von Limbeck points out - and my observations are in accordance with this view - is to be explained as due to some inflammatory or other condition, such as is ordinarily associated with an increase of leucocytes, complicating the illness towards its close. Ehrlich offers another explanation to account for the occurrence of this phenomenon).

(a) 2. Polynuclear Eosinophilic Leucocytosis. The recognition of such a leucocytosis is of comparatively recent date. Gollasch was the first to observe that in a patient suffering from asthma there was present in the blood a large increase of the eosinophilic cells. Later Neusser observed an increase of these cells in the blood in a patient suffering from pemphigus, and Canon in chronic skin diseases. Zappert has recently made a very complete study of the behaviour of these cells in many pathological conditions.

Ehrlich understands by eosinophilia a one-sided increase of the polynuclear eosinophile cells in the blood. This observer further says that no difficulty should exist in distinguishing between this condition and leukaemia, the latter condition being accompanied by a number of other characteristic changes; -yet

yet one must not, as has been stated, regard the presence of mononuclear eosinophilic cells as diagnostic of leukaemia, for these are occasionally to be found also in ordinary leucocytosis.

The increase of these cells is not only a relative one but an absolute. This form of leucocytosis is found under the following conditions :-

1. In bronchial asthma. - Here the percentage of eosinophilic cells may be increased up to 10 - 20%

2. In pemphigus. - In this affection the number of eosinophilic cells is often highly increased. Zappert found in one case 4800 eosinophiles per c.m/m. as compared with the average ~~figures~~ 200.

3. In acute and chronic skin diseases :- Canon found the eosinophiles increased in a great variety of skin diseases e.g. prurigo, psoriasis. Canon believes that the increase in the number of eosinophiles is less dependent on the nature of the disease or its local intensity than on the extent of the affection. In one case of acute urticaria observed by myself the eosinophiles numbered 15% of all the leucocytes; in another case observed by A. Lazarus they composed 60% of all the leucocytes.

4. In Helminthiasis, (According to Müller and Rieder, Zappert Leichtenstern, T. R. Brown, and others)

5. In Post-febrile conditions. - A moderate increase in the number of eosinophiles takes place after the fall of the temperature in most acute inflammatory -conditions

conditions accompanied by leucocytosis, as has been pointed out by many observers.

6. In malignant tumours. - According to the observations of Reinbach - and those coincide with my own - an increase of eosinophiles is only occasionally to be met with in tumour cachexia.

7. Compensatory Form (after extirpation of the spleen - Ehrlich).

(b) Leukaemia ("Mixed Leucocytosis")

Ehrlich says this disease may be subdivided from a haematological standpoint thus :-

1. Leukaemic process due to the proliferation of lymphoid tissue: "Lymphatic Leukaemia."

2. Leukaemic process due to the proliferation of the myeloid tissue : "Myelogenous Leukaemia."

The accompanying clinical phenomena could be stated simply thus, e.g. "Lymphatic leukaemia with enlargement of the liver or of the spleen ", "myelogenous leukaemia with enlargement of the lymph glands".

Ehrlich goes on to describe the blood condition found in those two forms and asserts with good evidence, in opposition to v. Limbeck that in all cases from the examination of the blood alone leukaemia can be diagnosed from the ordinary forms of leucocytosis. As however in the great majority of cases no difficulty is experienced in differentiating be-

-tween

tween these conditions I need not enter more fully into the subject here.

Chapter VIII

Theoretical Conception of LEUCOCYTOSIS.

A. The Polynuclear Finely granular Leucocytosis.

1. The Theories in Detail.

The theory of Virchow, who regarded the occurrence of leucocytosis as due to irritation of the blood-forming organs, and the views of the other older observers have already been referred to under the head of Inflammatory Leucocytosis. We are now placed in a better position to examine the later theories advanced on the subject.

The fact that after the taking of nourishment, the administration of certain drugs, or under the influence of an acute infection, the number of white cells in the blood is greatly increased, has long been known. Von Limbeck was the first however to regard these different phenomena from a common point of view as due to the action of chemotactic-working substances. In the last edition of his Clinical Pathology of the Blood (1896) he expresses himself as follows :-

"My clinical and experimental observations had at that time lead me to expect an intimate relationship between Inflammatory Leucocytosis and the formation of exudation, and although certain later observations

-have

have gone to show that a leucocytosis can also occur without exudation, wide experience has corroborated the fact that, clinically at least, for the majority of cases my assumptions have proved true ..... Indeed according to the amount and the kind of the virus introduced (such was my opinion) the organism reacts. Whether it is a question of pus producing bacteria or the products of metabolism of these, the amount of the exudation, as is also the leucocytosis, is dependent on the virulence of the former or the quantoty of the latter. The increased number of leucocytes launched into the blood-stream occurs, according to my former conception, in consequence of the unexplained chemotactic action of the products of those organisms or other substances poured into the blood-stream out of the organs; the leucocytes are also partly deposited as an exudate at the place of the established inflammation. "(Vide l.c. p 244).

"Löwit advanced a theory contrary to this. He found that after the injection of certain substances, e.g. pepsin, hemi-albumose, leech-gland extract, nuclein, uric acid, tuberculin, etc. a marked diminution of the leucocytes in the circulating blood took place; this diminution was followed at a later period by an increase of these cells. The hypoleucocytosis he regarded as being due almost entirely to a destruction of the corpuscles, a leukolysis. The products of destruction by their irritative

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action cause an increased influx of young leucocytic elements from the blood-forming organs into the blood-stream and so at length bring about an increased number of leucocytes in the blood: thus, according to Löwit, is the hyperleucocytosis produced.

The third theory of leucocytosis is that associated with the names of Römer and Buchner. According to these authors it is not the metabolism products of the micro-organisms, but the proteids contained in the bodies of the bacteria themselves, which, when they are set free in the tissues of the body, exercise a direct irritative influence. Römer further contends that this increase of leucocytes is not to be referred to an increased emigration of these out of the body tissues into the blood-stream but regards the increase as due to an amitotic division of the cells themselves, the multiplication taking place principally in the small veins.

A fourth theory emanates from Schulz. According to this author on the ground of certain experiments conducted on rabbits, none of these theories hold good. He disallows the occurrence of an absolute increase or diminution in the number of the haemic leucocytes, and makes an unequal distribution of these cells in the blood-stream accountable for these appearances.

Goldscheider and Jacob as the result of a long series of experiments were able to corroborate

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the occurrence of a hypoleucocytosis followed by a hyperleucocytosis on the injection of certain substances subcutaneously and intravenously (hemialbumose, spleen and bone marrow extracts). These authors were however unable to confirm the occurrence of a leucolysis in the sense of Löwit. During the stage of hypoleucocytosis they found the capillaries and small vessels of the lungs abnormally full of leucocytes, mononuclear as well as polynuclear, but the latter especially preponderating. In the stage of hyperleucocytosis the capillaries of the lungs contained a still higher number of leucocytes and the majority were polynuclear. Signs of leucocytic destruction were not present. They therefore conclude that the hypoleucocytosis rests on this circumstance, that the leucocytes - especially the polynuclear as it appears - are driven into the capillaries and small vessels and therein are held fast.

Again, according to these authors, the subsequent hyperleucocytosis cannot be explained as the return of the leucocytes from the lung into the general blood-stream, as in this stage they found the capillaries of the lung more richly packed with leucocytes - mostly polynuclear - than in the previous stage. The occurrence of the hyperleucocytosis would thus be explained by them : the material injected passes over into the lymph vessels, and attracts an increased num-

-ber of

ber of white cells into the blood stream; they consider it probable that the augmentation in the number of white cells is due only in a slight degree to new formation of leucocytic elements, but think that the hyperleucocytosis results from this circumstance, that in the blood-forming organs especially the bone marrow there are rich stores of leucocytes, especially polynuclear elements and that these so held ready in reserve, are poured forth into the blood-stream. Further they regard the processes of hypo- and hyperleucocytosis as independent of each other.

They have proved Schulz' conclusion wrong: during the stage of hypoleucocytosis the white blood corpuscles are not driven from the peripheral vessels into the heart and large vessels; during the stage of hyperleucocytosis the capillaries of the skin are not highly enriched with leucocytes at the expense of the vessels of the internal organs. They have also shown that Römer's assertion, that the injected substance caused a direct new formation of white blood cells in the venous system, is incorrect.

Their findings agree with those of Löwit that in cases of well marked hypoleucocytosis almost exclusively mononucleated cells are to be met with, and that gradually in the course of the hyperleucocytosis a decided increase of polynucleated cells occur. They however believe, contrary to Löwit, that the polynucleated cells do not develop from newly imported

-mononuclear

mononuclear cells, but are due to an increased inflow of the white cells which are held in reserve in bone marrow (polynuclear), and which are poured out in increased numbers into the blood-stream as the result of irritative chemical action.

They find no direct connection between exudation formation and leucocytosis as v.Limbeck would assume unless the amassing of the leucocytes in the capilaries be considered as such. These authors refer the phenomena of hypo- and hyperleucocytosis to the influence of chemotaxis. To Pfeffer we are especially indebted for our knowledge of chemotaxis. V. Limbeck, Hüppe, and Hertwig were the first to extend the conception of chemotaxis to augmentation in the number of leucocytes occurring in the blood-stream, and regarded leucocytosis as the result of a positive chemotaxis. This conception among others, Buchner, Römer and Rieder accepted, and Joas and Löwit opposed. Goldscheider and Jacob, resting their assumptions on the theory of Hertwig, declare that (given a like reaction susceptibility of the individual) it is dependent on the degree of concentration in which the substance under consideration is brought into the tissues, whether it shall produce an attracting or repelling action on the leucocytes. The following conclusions they deduce from their experiments :-

"I. If we introduce a substance in very
-small

small doses into the organism, especially into the blood-stream, the repelling effect of these on the leucocytes in consequence of their slight degree of concentration will be very slight. If now we repeat these small doses in certain time intervals, so appears gradually the attracting effect even more prominent, every single injection effects a known iirritation on the blood-forming organs, and so will we arrive at, as a final effect, a considerable hyperleucocytosis.

" II. If now we repeat a moderately large concentrated dose, the capillary-attracting action will first be produced on the leucocytes; these are impelled into the capillaries and therein held fast. Gradually the condition of things is changed; after sufficient time the material injected is distributed in the soft tissues, and lost its high degree of concentration and with it its repelling property, so that it can stimulate the blood forming organs partly to the output of new elements, partly to the giving up of elements already stored there.

"III. A third case is that in which we inject an excessively high dose. Here must naturally the repelling effect first of all be very great; but on the other hand we have injected so great a quantity of substance into the blood-stream that it must make its influence on the blood-forming organs appear after a relatively

a relatively shorter time. At first the newly imported cells are ever repelled and forced into the capillaries, but soon will the effect on the blood-forming organs be so powerful, that in a proportionately shorter time a condition of hyperleucocytosis comes to pass".

2. The Theories Discussed.

Of the above theories that of Schulz, which makes an unequal distribution of leucocytes in the blood-stream accountable for the phenomena of hypo- and hyperleucocytosis, has been shown not to be founded on fact. (Goldscheider and Jacob, Sémakine, Roncogliolo, and others).

Observers are likewise now agreed that it is not, as stated by Buchner and Römer, the proteins contained in the micro-organisms but much more the products of the metabolism of these whichare the active Agents in the essential production of leucocytosis.

The latter part of Römer's theory - the intravenous multiplication of leucocytes - has also been proved incorrect. (Löwit, Goldscheider and Jacob, and Kanthack).

Löwit in 1892 showed, that on the injection of certain substances into the blood-stream there occurred a great diminution of leucocytes in -the

the circulating blood and further pointed out that the hypoleucocytosis thus resulting was due especially to diminution in number of the polynuclear cells.

The occurrence of hypoleucocytosis following the injection of various substances was confirmed by a great many observers, but it was not generally agreed that the diminution in question was to be attributed to, as Löwit stated, leucolysis or a dissolution of the leucocytes. Goldscheider and Jacob (1894) corroborated the occurrence of such a hypoleucocytosis but referred the phenomenon to the negative chemotactic action of the material injected, which impelled the leucocytes into the capillaries of the internal organs, especially of the lungs. Werigo also believes that, on the intravenous injection of particulate matter, the leucocytes crowd into and remain for a time in the liver, spleen and lung. Everard, Démoor, and Massart find a hypoleucocytosis precede the leucocytosis induced by injecting subcutaneously and intra-peritoneally, in considérable quantity, bacterial cultures and culture fluids; and state that the leucocytosis thus produced was chiefly due to diminution in number of the polynuclear leucocyte. This they attribute not to destruction of the leucocytes, but to the leucocytes crowding into the blood-vessels of the liver, spleen, and marrow in virtue of chemotactic action.

Sherrington remarks upon the resemblance between injection hypoleucocytosis and the inflammatory hypoleucocytosis of his experiments in that the latter was also characterised by great relative diminution

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of the granular leucocytes and points out, as a possible factor in the occurrence of the phenomenon in his observations, the fact that the granular leucocytes tend disproportionately numerously to adhere and escape in the vascular region of the local inflammation.

Bruce, Müller and more recently Tschistovitch (1895), have also demonstrated a greatly increased number of leucocytes in the capillaries of the lungs and other internal organs during the stage of hypoleucocytosis; while Jacob in a still more recent paper (1897) confirms the results obtained in his former experimental work along with Goldscheider.

Further experimental observations go to corroborate the statement that the leucocytes are not destroyed. Solutions of peptone, of tuberculin, living cultures or filtrates have not been able to destroy the leucocytes in vitro. (Wright, Popoff, Tschistovitch).

In favour of the theory of leukolysis come first Löwy and Richter. These authors in 1895 stated that in rabbits during the stage of hypoleucocytosis an increase in the alkalinity of the blood comes about, which increased they refer to a destruction of leucocytes. Caro and Strauss found such changes not always demonstrable in the blood of man, a circumstance which Löwy and Richter explained by saying that in man

- a better

a better regulating mechanism allows no great variation in the alkalinity of the blood to take place. Further these same authors in a more recent paper (1898) declare that they have demonstrated in the blood during the stage of hypoleucocytosis an albumose reaction, a reaction which is never found in the normal condition, but is associated with a destruction of leucocytes and found in the blood and urine in cases of thoracic empyema, purulent bronchitis, and absorption of cell infiltrations, e.g. in erysipelas, pneumonia etc.

Botkin (1895) stated that in vitro leucocytes in the blood taken from pneumonia and typhoid patients much sooner became disintegrated than leucocytes from normal blood. He is of opinion that such destruction takes place in the circulating blood, that, in short, the leukolysis of Löwit is a true "leukocytolysis".

Notwithstanding these experiments the fact that the disappearance of an immense number of leucocytes from the circulation occurs almost instantaneously and leaves practically no trace behind combined with the overwhelming and insidputable evidence that in the period of hypoleucocytosis the capillaries of the lungs and internal organs contain an excessive number of white blood corpuscles, goes to show that the destruction of leucocytes, if such occurs is insignificant.

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The reason for such accumulation of leucocytes in the capillaries occurs, according to Goldscheider and Jacob in consequence of negative chemiotaxis; Stienon on the other hand asks whether it may not be due to a damaging action of the concentrated solutions injected on the endothelium of the pulmonary capillaries. Tschistovitch advances the following possible causes to explain the phenomena, viz.

1. Contraction of small arteries.

2. Increase of size along with diminished power of mobility of the leucocytes.

3. Chemotactic action of certain drugs.

4. Diminution of the strength of the heart.

After a longer or shorter period of time hyperleucocytosis follows the hypoleucocytosis. According to Löwit, who denies the influence of chemotaxis, the increase of leucocytes is due to the direct irritative influence of the products of the destroyed leucocytes on the blood forming organs which causes an increased output of white blood corpuscles into the blood stream. Horbacewski goes a step further and indicates nuclein as the special product of destruction which is the essential factor in the causation of a leucocytosis.

Whether it be the injected substances - as Goldscheider and Jacob believe - or the secondary disintegration products of leucocytes which are the direct agents in the production of an artificially

-raised

raised leucocytosis, it appears to me that in any case the phenomenon is essentially the same, viz. an attracting one on the leucocytes - an action which we term positive chemotaxis. It is by common consent agreed that certain substances outside the blood stream have power to attract leucocytes, and I believe, there is no reason to suppose that when introduced intravascularly this attractive force ceases to act.

If then hyperleucocytosis is due to be attributed to the action of positive chemotaxis, is hypoleucocytosis similarly to be explained as due to the action of negative chemotaxis? After intravenous injection the capillary network of the lungs is especially charged with the active principle injected, yet here are to be found the greatest accumulation of leucocytes. All Goldscheider and Jacob's findings, it appears to me, can be better explained by supposing that the hypoleucocytosis is produced by the action of a strong positive chemotaxis, which attracts the leucocytes in the circulation in the first instance to the lungs etc.; when the substance is diffused more equally in the blood after the lapse of time or due to a different method of introduction, it attracts into the blood fresh supplies of leucocytes and the occurrence of a hyperleucocytosis comes about.

v. Limbeck as the result of wide clinical experience had associated together exudation and leucocytosis. This connection Goldscheider and Jacob

-deny,

deny, because, they say, leucocytosis can occur also without exudation - a statement which is undoubtedly true. The first named author in the last edition of his book again affirms, that clinically at least, in the great majority of cases there exists a close connection between the two, and this statement is strongly corroborated by the results of the clinical observations of other investigators.

Further Winternitz experimented on a great number of organic and inorganic bodies especially with a view to determine whether such a connection existed between the local action on the tissues and the changes in the blood. He found that usually the height of the leucocytosis goes parallel with the intensity of the local action. The first group of bodies (salts and simple corrosives such as free acids and alkalies) provoked only slight leucocytosis with slight local reaction, and slight, transitory rise of temperature; on the other hand the so called true irritants (turpentine, oil of mustard, Croton oil, sapotoxin, digitoxin, silver nitrate, copper sulphate, compounds of mercury and antimony) besides aseptic suppuration produced as a rule a high degree of leucocytosis and high high fever generally lasting a few days.

V. Limbeck would no doubt have been able to supply the missing link connecting these two apparently somewhat contradictory observations had he not been led -astray

astray by his findings in certain experiments conducted by him on dogs. He injected into the knee-joint of these animals cultures of various kinds and found that the haemic leucocytosis preceded the exudation into the articulation; accordingly he regarded the cellular exudate as a result of the leucocytosis. Joas, as an outcome of his experiments, contradicts this statement and asserts that the emigration of cells in the mesentery of the frog must reach a high degree before the leucocytosis occurs. The leucocytosis can only be regarded as a secondary inflammatory phenomenon - according to him probably a regeneration phenomenon going beyond the requirements. Sherrington also, as the result of his observations regards this assumption of v. Limbeck's as being not in accordance with the truth. From a number of his experiments Sherrington "would conclude rather the reverse, because the blood became obviously apoplasmic prior to any increase of the number of leucocytes in it".

3 Conclusions

Keeping in view the clinical facts and also having regard to the apparently somewhat contradictory experimental work, what explanation can be offered regarding the supposed intimate connection between leucocytosis and exudation.

The answer, I believe, is simple : common leucocytosis and exudation owe their origin to the

-same

same cause, - chemotaxis. Haemic leucocytosis is the result of haemic chemotaxis; exudation or local leucocytosis is the result of local chemotaxis.

1. If a positively acting chemotactic substance is introduced directly into the circulation the leucocytes will ~~relatively~~ naturally be attracted into the blood stream; ~~as~~ no exudation will occur because the attracting force is intravascular,

2. If introduced into the organism extravascularly it will tend to cause a leucocytosis in the neighbourhood of its introduction. Its power to produce a haemic leucocytosis will depend on the facility with which it is absorbed into the blood stream. If rapidly and completely absorbed, the local exudation will be slight. On the other hand, as is the case in most inflammatory conditions, if the local chemotactic substances are being produced continuously a local leucocytosis will result, but further, the attracting substance passes over into the blood stream and causes the immigration of white corpuscles from the leucocyte producing centres and thus a haemic leucocytosis comes about.

3. Clinically in the vast majority of cases a haemic leucocytosis indicates the occurrence of a local leucocytosis. (The haemic leucocytes may be regarded as being in transit to the site of the established inflammation and emigrating at this situation

-because

because the attracting force is greatest and situated extravascularly in the tissues in this region).

4. An acute local leucocytosis of any extent cannot occur without evidence of such being present in the blood of the general circulation.

5. The cells present in the exudate are similar to those which are specially increased in the haemic leucocytosis.

6. The increased number of cells present in the blood are supplied from the reserve stores in the bone marrow. The bone marrow is further stimulated to the production of fresh supplies of polynuclear cells should the conditions producing the leucocytosis last for any considerable period of time.

B. The Polynuclear Coarsely Granular Eosinophilic Leucocytosis.

Ehrlich believes that the neutrophilic and eosinophilic cells are of different chemotactic reaction.

His explanation of the phenomena associated with eosinophilic leucocytosis very closely agrees with my conclusions as to the occurrence of the neutrophilic leucocytosis, (the first five of which were written before his observations were published) and also my views regarding the leucocytosis of pneumonia

-set

set forth in my Gunning Essay of two years ago.

I translate his words :-

" In the vesicles of pemphigus a substance is present which attracts through chemotaxis the eosinophiles; thither wander the eosinophiles present normally in the blood, and produce an eosinophilic suppuration..... If the disease is widespread, under these conditions through absorption and diffusion a large quantity of the specifically acting substance passes out into the blood-stream and exerts from here a strong chemotactic action on the physiological store-houses of the eosinophiles, and causes a more or less high increase in the number of eosinophiles in the blo blood.

" The bone marrow, according to recognised biological axioms through the increased output is incited to increased new formation and thus continues to be able to maintain a condition of eosinophilia during the course of an affection of considerable duration."

Ehrlich further adduces weighty evidence in support of his statement that the direct cause of eosinophilia lies in tissue destruction and the products resulting therefrom.

PART II

THE LEUCOCYTOSIS OF PNEUMONIA.

Chapter IX

Observations of the different Writers on the Subject.

Of all inflammatory affections attended with leucocytosis the one that has attracted most observers is croupous pneumonia, and those who have studied the disease from the standpoint of the blood are unanimous in their opinion that it is attended in the great majority of cases with marked increase in the number of colourless corpuscles.

Piorry early in this century had remarked on the so called "Buffy Coat", "Crusta Phlogistica" of the blood of the pneumonic patient, a phenomenon usually observed towards the seventh or eight day of the disease, and refers its occurrence to a ~~spher-~~ special ~~ical~~ feature of the disease,- viz."Haemitis."

Masse noted in ~~phenomena~~ pneumonia a distinct increase in the number of the white cells. Virchow makes a li like observation and attributes the occurrence of the continued leucocytosis to a swelling of the bronchial lymph glands, assuming that in cases where those glands do not swell there will be observed no leucocytosis. This conception Sadler showed to be incorrect, for in certain cases of pneumonia, which during life showed a marked degree of leucocytosis,

- after

after death the peribronchial glands were found to be anthracosed and atrophied.

Of more recent observers first in order come the names of Sörensen, Boeckmann, Halla, and Hayem and Gilbert, and later among others those of Tumas, v. Jaksch, v. Limbeck, Pick, Pée, Rieder, Maragliano, Tschistovitch, Kikodze, Laehr, Sadler, Biegański, Klein, Ewing, Billings, Cabot, Stiénon, and Türk .

Boekmann found not only in pneumonia but in other diseases accompanied by fever during the period of high temperature a marked increase of leucotytes and a proportionate decrease of the red blood corpuscles and came to the following conclusions: in acute feverish diseases the count of the red blood cells is inversely proportional to the degree of the fever, and the count of the white corpuscles is directly proportional to the same.

In the cases of pneumonia reported by Halla leucocytosis only twice was absent and both were very severe cases which terminated fatally, of the other 12 cases only 3 died. The leucocytosis, although usually diminished in degree, frequently outlasted the crises by one or moer days.. The intensity of the fever does not usually affect the leucocytosis. Reinert agrees with the views of Halla.

Hayem and Gilbert reported that in two cases of typhoidal pneumonia (la pneumonie typhoïde) - there was

there was observed no close fibrinous reticulum or increase in the number of white blood corpuscles such as is characteristic of ordinary cases of acute pneumonia. Hayem later declares that the increase of the white cells in pneumonia in general goes parallel with the development and the different phases of the disease. In cases of slight severity the leucocyte count is from 8000 - 12000 ; in cases of medium severity the count reaches 18 - 20,000. Only in severe cases may the leucocyte count reach higher, and Hayem in a csse of acute pneumonia which terminated fatally counted 36,000 white corpuscles per cubit millimetre. With the decline of the disease the leucocyte count diminishes gradually or suddenly; generally there occurs a sinking under the normal before the physiological standard is finally arrived at. Hayem believes that, in those severe typhoidal cases of pneumonia in which the inflammatory changes in the blood (i.e. increase in the number of white corpuscles) are absent up till death, exudation is trifling and a minor feature in the case. Further he accentuates the fact that the inflammatory changes in the blood are pre-eminently associated with exudative diseases.

According to v. Limbeck and Pick the leucocytosis comes on early in pneumonia, persists during the whole course of the febrile period and disappears at the crisis. Pick has observed one case where the leucocytosis was preceded by the diminution in the number of leucocytes.) The parallel between the leu-

- cocytes

cocytes and the temperature is however not always so constant, for in some cases the leucocytosis outlasts the fever by a few days, although as a rule there is a marked diminution of leucocytes observable shortly before the occurrence of the critical fall of temperature; in the case of a lysis there may be observed a gradual decrease in the number of the leucocytes. If a so-called pseudo-crisis occurs in the course of the affection it is accompanied by no diminution in the number of white cells.

V. Limbeck has observed in cases terminating fatally an increase in the leucocyte count towards the end. There are also to be observed cases of croupous pneumonia, in which during the whole course of the disease leucocytosis is absent. These are said to furnish a worse prognosis. Limbeck however comes to the conclusion after studying the experimental work of Tschistovitch and reviewing the clinical literature on the subject that the appearance or non-appearance of leucocytosis in pneumonia affords no sure prognostic sign regarding the course of the disease. A direct dependence of the degree of the leucocytosis on the extent of the infiltration in the lungs does not exist; on the contrary it depends clearly on the degree of virluence of the infecting material and the constitution of the infected organism.

According to Tumas the increase of the white blood corpuscles outlasts the crisis by about one to

- three

three days.

Pée gives expression to his astonishment at the high degree of leucocytosis occasionally found in pneumonia.

Von Jaksch finds a relatively greater leucocytosis in the case of children suffering from acute pneumonia than in adults affected by the same disease. He has lately observed that the progress in cases of acute pneumonia running its course without an increase in the number of white blood cells is very unfavourable. He believes that where there is an absence of leucocytosis in cases of severe croupous pneumonia, means for the increase of the leucocytes by the administration of drugs (antipyrin, antifebrin, pilocarpin, nuclein,) should be adopted. In one of his cases a day after the administration of pilocarpin an increase of leucocytes was apparent.

On the other hand Pichler has still more recently reported the result of the effect of pilocarpin, nuclein, and antipyrin on the count of the leucocytes in pneumonia and typhoid fever, Twenty-four cases of pneumonia were observed. Neither the administration of policarpin nor nuclein was invariably attended by an increase in the number of leucocytes; nuclein however usually caused an increase. When a rise occurred the number only exceptionally reached a high figure. In the case where antipyrin was tried, observations showed a sinking in the number of the white

- cells.

cells. Pichler's conclusion is that, as a spontaneous high degree of leucocytosis, so also the artificial increase of leucocytes, in no way warrants a favourable prognosis. Similar results were arrived at as regards typhoid.

Sadler has recently observed 21 cases of pneumonia in the clinique of v. Jaksch. In 16 of these cases there was a leucocytosis and 3 died. In 5 cases there was no leucocytosis . Three of them died and the sectio showed in two of these cases infiltration of both lungs, in the third case nearly the whole of the left lung. In the cases which recovered the fall in the leucocytosis corresponded to the fall in the temperature.. The count of the red blood corpuscles in most of the cases was normal, the haemoglobin in all cases where the red blood corpuscles were normal in amount was perceptibly diminished.

Tschistovitch, as the result of clinical and experimental observations, also regards diminution in the number of leucocytes as an unfavourable prognostic sign, and refers the occurrence of death in cases of pneumonia accompanied by high leucocytosis to localisation of the affection in especially vital organs (meninges, endocardium), or to very extensive infiltration of the lungs.

Kikodze states the relative and absolute increase of the white blood corpuscles to be about twice up to three times the normal.. Only in severe

- cases

cases in which death resulted could he find no increase of the same. According to this observer the leucocytosis appears before the change in the lung (? is apparent) and remains up till the crisis. The rise in the number of leucocytes is accounted for by the great increase in the mature (polynuclear) leucocytes, which according to Kikodze's view become mature in the lung alveoli - Simultaneously with the temperature crisis there comes a blood crisis in which a fall of the leucocytes takes place to or below the normal level.

Maragliano finds no relationship between the intensity of the leucocytosis and the severity of the infectious disease. He does not agree with the shortly expressed opinion that leucocytosis betters the prognosis in pneumonia. He has seen pneumonia patients with a high degree of leucocytosis (of over 40,000 leucocytes) die, while others without leucocytosis have recovered. He further regards it as useless to artificially promote leucocytosis in those cases where none exists. His views are thus in accordance with the before mentioned later observations of Pichler.

L. Raehr finds an unmistakable connection between the temperature and the leucocytosis in this, namely that the acme of the fever shows the highest leucocytosis; at the fall of the temperature there occurs -

occurs a quick fall of the leucocytes. He cannot agree, along with Halla, Reinert and v. Limbeck, with the assumption of Boekmann's that the degree of the leucocytes is dependent on the height of the fever. In numerous cases where pseudo-crisis occurred the leucocytosis still continued. Of his 16 cases all showed leucocytosis and 2 died. As regards the variation in the relative proportions of the different varieties of white cells, the polynuclear forms are increased, the eosinophilic cells relatively diminished. The number of the red corpuscles and the percentage of haemoglobin sink during the course of the disease to rise again to normal after the crisis.

Rieder reports the results of observations on 26 individuals of different ages and sexes. He finds no parallel exists between extent of the infiltration and the degree of the leucocytosis in the different cases observed by him. Further in the self-same case with increase of infiltration of the lung, an increase of the leucocytes in the blood cannot always be detected. He corroborates the statements of other observers that the leucocytosis appears early. In three cases Rieder was able to make blood examinations within 6,14, and 16 hours respectively from the occurrence of the rigor and found at that period in all three cases a very high degree of leucocytosis. The fall in the temperature curve took place in almost all the cases recorded by him prior to the fall

- in the

in the leucocyte curve. He also gives a few cases of croupous pneumonia in which the total leucocyte count is compared with the relative proportion of the different forms of leucocytes present. The eosinophilic cells could only in one case of pneumonia be observed. Rieder adds that it ought not be said on this account that they are generally deficient in this disease, but that only on account of the increase of the other forms is there observed a relative diminution of these. The percentage ratio of the mononuclear sank varying from 4.4 %(17600 leucocytes in one c.m.m.) to 17.3 % (29200 in 1 c.m.m.). One sees in this connection, he goes on to say, that no parallel can be drawn between the leucocyte count and the percentage increase of polynuclear cells in the blood; when also a rare case is met with where no noteworthy increase is observable in the leucocyte count, there is yet observed in the blood the characteristic condition found in leucocytosis, - decrease of the eosinophilic and increase of the polynuclear cells. That in lethal terminating cases the leucocyte count steadily rises, he holds to be incorrect, on the other hand he found in such cases often an especially trifling leucocyte increase. From the height of the leucocytosis can be drawn no definite conclusion as regards the prognosis, but for the differential diagnosis he judged the blood exam-

- ination

inition to be of great value.

Monti and Berggrün found in children in all cases observed by them a well marked, sometimes high leucocytosis (to 55000). The leucocytosis is leased according to those writers in the early stages of the affection; it increases with the extension of the pneumonia; the degree of the leucocytosis during the course of the disease is therefore andindication for judging the severity of the affection. The leucocytosis diminishes as soon as resolution of the infiltration commences. Rapid diminution is an objective indication by which one is able to foretell a quick recovery; while a slow fall points to a protracted resolution. If a progressive diminution of the leucocyte count occur with continued fever, so may one expect the crisis to happen in the next day or so, if on the contrary the leucocytosis increases, without the process demonstrably extending, at least an extension of the process is to be expected.

Biegański found in 11 of 13 cases examined by him a marked leucocytosis. In one case which at the beginning showed a leucocytosis, there occurred a diminution of the leucocyte count to below the normal before the lethal exit, and in another case which terminated in death a preceding hypoleucocytosis. The highest leucocyte count is found immediately before the crisis; thereafter there occurs a diminution

- of the

of the leucocyte count to or below the normal. Generally this diminution occurs in crisis fashion, only in cases where the temperature falls by lysis is there likewise a gradual sinking of the leucocyte count. In cases of pseudo-crises no change in the leucocyte count occurs. In cases of delayed resolution the leucocytosis remains longer than the fever. Small rises of temperature after the crisis have no influence on the leucocyte count. The failure of leucocytosis in pneumonia is of no great prognostic signification, for there occur cases which run a favourable course, in which at the commencement no leucocytosis occurs, but where at a late stage leucocytosis appears, and vice versa. The presence of leucocytosis with a fall in the temperature does not necessarily indicate a pseudo-crisis. At the beginning of the affection where yet no signsof infiltration are manifest, leucocytosis is of diagnostic signification.

Kühnau found a leucocytosis in pneumonia which was not proportional to the extent of the infiltration. On the other hand he regards the failure of the leucocytosis as a bad sign.

Smith regards those cases of pneumonia in which leucocytosis is present as being ~~pneumonia~~ prognostically better than those in which there occurs a very slight increase or indeed a diminution of leucocytosis.

Ewing in 101 cases found leucocytosis absent - in six;

in six; six died.

Billings reports 22 cases; one had no leucocytosis and died. He finds no strict proportion between the height of the fever and the leucocytosis; but as the temperature falls so falls the leucocytosis, the leucocytes generally reaching normal 48 hours later than the temperature. When both lungs are affected the leucocytosis reaches a very high degree. In delayed resolution the leucocyte count continues high for a lengthened period . The leucocytosis is due entirely to increase of the polynuclear cells.

Cabot believes the degree of leucocytosis is probably the resultant of two forces, viz.: the severity of the infection and the resisting power of the individual. "Nevertheless", he continues, "cases with extensive signs in both lungs are more apt to have very high counts, provided the 'reaction" of the patient against the infection is vigorous. The cases appear to fall into the following groups as regards the degree of leucocytosis present.

1. Mild infection, vigorous reaction = slight leucocytosis.

2. Severe or moderate infection, vigorous reaction = marked leucocytosis.

3. Severe infection, feeble reaction = no leucocytosis".

He notes further that the patients in class 3 almost invariably die; there is not sufficient of a
- struggle

struggle to raise the leucocyte count. Where either the patient or his disease easily gains the mastery there is no leucocytosis or a very slight one; but in the much larger class of cases in which the struggle is a fierce one, leucocytosis appears, which-ever way the struggle results. In the Massachusetts General Hospital 229 cases have been studied. Eighteen of these presented no leucocytosis at any time, and of these 18, 17 died and the other one seemed moribund but finally recovered.

What Osler says in the second edition of his text book on medicine may be perhaps be taken as a fair resumé of the opinions of the majority of observers on the subject :-

"Anaemia is rarely seen. There is in most cases a leucocytosis, which appears early, persists, and disappears with the crisis. The leucocytes may number from 12 to 40 or 50,000, even more per c.m.m. The fall in the leucocytes is often slower than the drop in the fever, particularly when resolution is delayed. Of considerable prognostic importance is that in malignant pneumonia, the leucocytosis is absent; and in any case the continuous absence may be regarded as an unfavourable sign. A striking feature in the blood-slide is the richness and density of the fibrin network. This corresponds to the great increase in the fibrin elements, which has long been known to occur in pneumonia, the proportion rising from 4 to 10 parts per thousand. Hayem describes

- the

the blood plates as greatly increased.

Although abundant observations have thus been made on the variation of the total number of leucocytes occurring in the blood of the pneumonic patient from day to day the changes which take place during the same period in the relative numbers of the different forms of these cells have been but little investigated. It is true that it was affirmed and generally admitted that the polynuclear cells are increased, the eosinophilic cells diminished during the course of the affection, but little, until quite recently, was known regarding the period and mode of that increase, the time and degree of that decrease and the subsequent return to normal. -

Stiénon, in a paper published in the Annals of the Royal Society of Brussels for the year 1895 and brought quite recently under my notice, gave a long series of observations on the percentage ratio of the different varieties of leucocytes in pneumonia. As however relatively few of the observations were made during the acute period of the disease, the total number of leucocytes per c.m/m. of blood was not (except in one or two solitary instances) ascertained, and no record is given of the temperature or the chief clinical features of the disease, his paper is not of such value as might at first sight appear.

Quite otherwise are the careful researches of Türk. To these and the observations of the other workers on this special department I shall refer when - I state

I state the result of my own work on the subject.

Chapter X

Original Observations.

My observations were directed to the daily comparison of the total with the relative numbers of the different varieties of the leucocytes during the course of the attack, and the further comparison of the figures obtained with the main clinical facts in each case. The expectation was entertained that thereby more light might possibly be thrown on certain points connected with inflammatory leucocytosis not yet clear, and possibly some information gained in regard to the life history of the leucocytes themselves and the mutual relationship of the different forms of the cells.

Towards this end the following methods were adopted. The total number of leucocytes per c.m/m. was first ascertained by means of the Thoma-Zeiss leucocyte pipette and counter-according to the degree of leucocytosis the blood was diluted 10 or 20 times. (As a rule where it was expected that the count would exceed 15,000 it was found more convenient to use the latter dilution.) The diluting fluid was the ordinary solution of methyl-green with .3 % acetic acid. The number of leucocytes on 400 squares of the counter (= $^1/_{10}$ c.m/m. of the diluted fluid) was ascertained, and that number multiplied by

- one or two

one or two hundred according to the dilution ; this gives sufficiently accurately the number of white blood corpuscles per c.m.m.

Cover-slip preparations of the blood were also taken at the same time. As a rule these were allowed to dry in the air and afterwards fixed by heat corrosive sublimate or other fixing reagent. In certain cases where it was specially desirable to have the cells as little altered as possible the films were immediately placed in the fixing solution. The films were stained in a variety of ways. In the majority of the preparations however either haematoxylin and rubin and orange or methylene-blue-eosin stains were used; in some of the later observations the quick method recently recommended by Gulland was employed. The forms of cells normal to the human blood differentiated by me were four in number :-

(1) Polynuclear,

(2) Large mononuclear and transitional,

(3) Lymphocytes,

(4) Eosinophilic.

(In the cases and charts these groups are respectively denoted by the letters, P.,LM, LY, E.)

Although in my earlier observations many more were enumerated, I afterwards found it necessary only to count on an average 300 cells in order to calculate sufficiently closely the percentage ratios of the different forms. Where however the percentage ratio of cells occurring in very small numbers e.g.

- eosinophililes

eosinophiles, was required to be accurately estimated a very much larger number of corpuscles was counted. When the preparations examined showed anything especially noteworthy or the presence of abnormal cells all the available cover - slips were variously treated and studied carefully under the microscope.

Appended to ~~this part of~~ this thesis there are to be found collected in tabular form the records of 23 cases of acute pneumonia with the results of my observations on the leucocytes in each case. The total number of white cells is reported and in succeedingcolumns the relative percentage of the polynuclear, large mononuclear cells, lymphocytes, and eosinophiles to the total number of leucocytes in the blood of the general circulation is shown.

A. General Survey of the Cases.

Of the twenty-three cases of pneumonia examined by me and fully recorded in this thesis, twenty were accompanied by a leucocytosis and 5 died; three cases were accompanied by no leucocytosis and all three died.

Of the five deaths in cases accompanied by leucocytosis Case 16 was one of so-called traumatic pneumonia in an alcoholic subject, it was complicated by very extensive acute pleurisy. In the next two cases there was no section. In one the clinical examination pointed to consolidation of the whole of the

- right

right lung, and possibly right-sided empyema. The other was complicated by right-sided hemiphlegia with aphasia (? cerebral thrombo-sis/ occurring during the course of the pneumonia ; the leucocyte count in this case was the highest of those terminating fatally, viz.,30,000, which number remained for three days practically stationery, never showing any marked variation up to within a short time of death. Case 19 revealed acute pericarditis with effusion. Case 20 showed grey hepatisation of the whole of one lung, but no changes of importance in any of the other organs.

Of the remaining 15 cases occurring with leucocytosis, two of them were peculiar in this, that the leucocytosis which was present at an early stage, disappeared for 2 to 3 days during the acute stage, reappeared just before the crisis, again to decline with the fall of the temperature. In one case (the first of the series) the patient was extremely weak and collapsed during the stage of no leucocytosis and coincidently with the rise in the numbers of the leucocytes his condition improved. The second patient in which this phenomenon occurred was a boy aged 13 (case 4) whose condition did not at any time afford ground for anxiety ; he had had an attack of croupous pneumonia a year previously.

Of the other cases ten made a good recovery, while in three convalescence was delayed owing to such complications as pleurisy with effusion and empyema (cases 13, 14, 15,).

- Three

Three patients showed no leucocytosis and death occurred in each case . The first of these (Case 21) was that of an alcoholic patient whose condition moreover at the time of the blood examination, (performed a few hours before death), apart from slight tremor of the tongue, was not such as in any way to indicate a speedy lethal exit ; the sectio revealed the lower lobe of the right lung in a state of grey hepatisation. Case 22 was that of a patient bed-ridden for some months suffering from a cerebral tumour ; the sectio showed only a small amount of consolidation. Case 23 was like the first that of an alcoholic patient in whom the pneumonic attack was accompanied by delirium tremens and the post-mortem examination showed consolidation of the whole of one lung. I shall refer more particularly to the result of the blood examination in these cases at a later stage.

B. Changes in the Total Number of Leucocytes.

1. Is the leucocytosis preceded by hypoleucocytosis?

Rieder has asserted that the leucocytosis of pneumonia begins early, within a few hours after the occurrence of the rigor. V. Limbeck states that leucocytosis commences prior to the occurrence of the

- exudation

exudation, an assertion questioned by Joas and Sherrington. Löwit would expect a diminution in the number of leucocytes in the circulating blood to precede the leucocytosis. Sherrington has shown experimentally that such a phenomenon occurs at an early stage after the establishment of the lesion in non-bacterial inflammations of an acute local character. Everard and Démoor state that, according to their experience, when the human body or the animal organism is invaded by infection one sees habitually a first stage, characterised by an intense hypoleucocytosis, this stage coincides with the onset of the attack, and perhaps lasts for some hours. Owing to its short duration it may perhaps pass unperceived. To this stage succeeds hyperleucocytosis. Stiénon questions this assertion and notes that the methods of observation of those authors are defective, in that, instead of making an absolute count of the white cells, they reckon the relative proportion of these to the red corpuscles. I believe, though I have not been fortunate enough to get a case sufficiently early, that a hypoleucocytosis of lesser or greater degree may occur at the commencement of many cases of pneumonia. The grounds for such an assertion will ~~have to~~ be given later.

2. Time of onset and duration of the leucocytosis.

The condition of leucocytosis, or hyperleucocytosis as it has also been termed, accordingly comes on early in pneumonia. In most cases it persists

- during

during the whole course of the affection. In my observations it outlasted the fever from one to six days. The decrease of the leucocytes is generally tardy iin those cases in which there is no sudden and complete fall of the temperature to normal, ot where, this occurrence having taken place, the temperature curve thereafter shows certain minor elevations above n normal. In other words, in those cases in which the temperature curve falls by crisis the leucocyte curve falls by lysis ; and in those cases in which the former falls by lysis, the latter also falls by lysis, the fall however being more protracted than the other.

See Charts I. II. III.

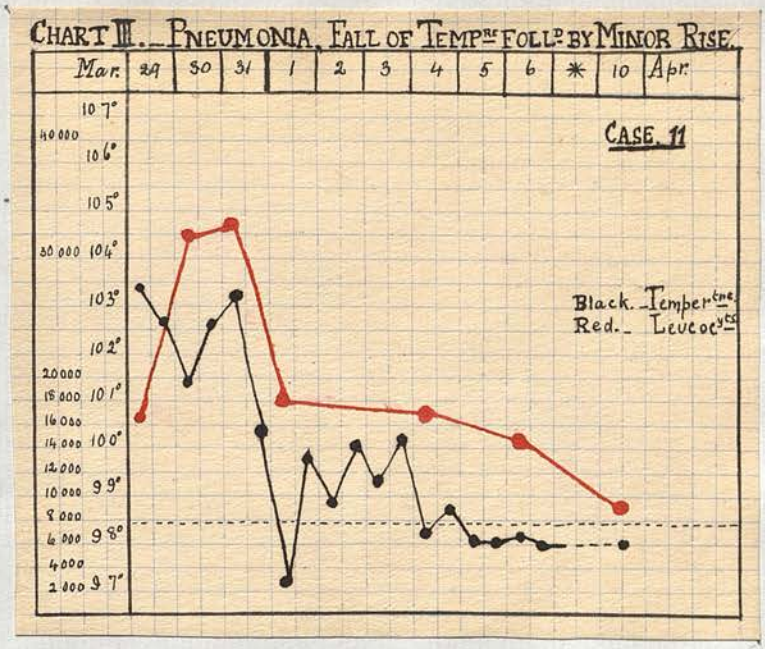


CHART III. PNEUMONIA. FALL OF TEMPre FOLLd BY MINOR RISE.
Mar. 29 30 31 1 2 3 4 5 6 * 10 Apr.
CASE. 11
Black. Temperture
Red. Leucocytes
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
40000
30000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000

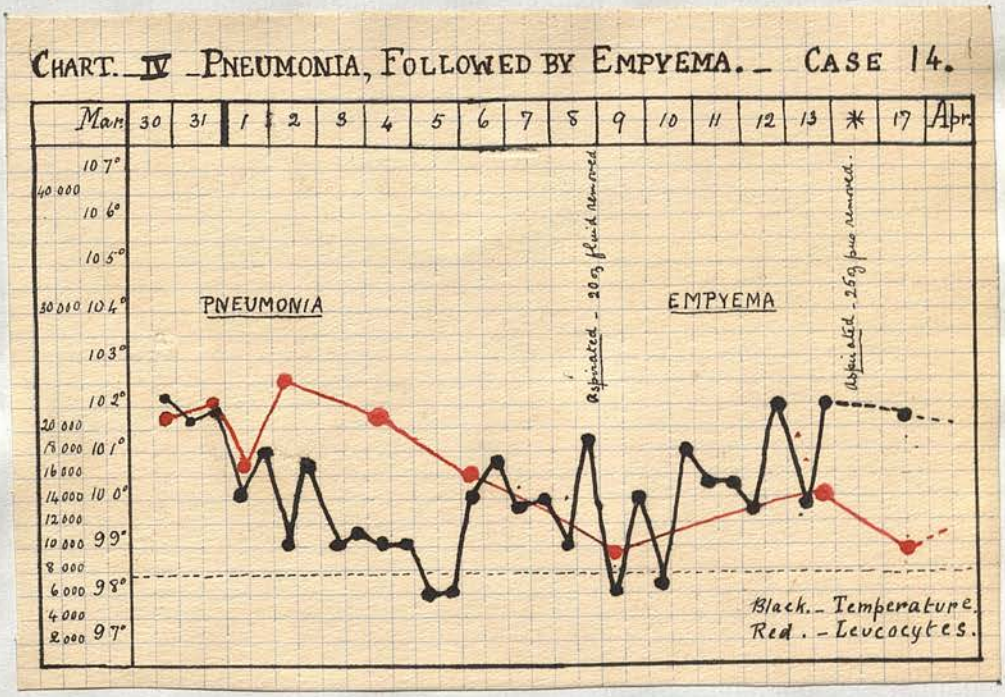


CHART. IV PNEUMONIA, FOLLOWED BY EMPYEMA. CASE 14.
Mar. 30 31 1 2 3 4 5 6 7 8 9 10 11 12 13 * 17 Apr.
PNEUMONIA
EMPYEMA
Aspirated - 20 oz fluid removed.
Aspirated - 25 oz pus removed.
Black. Temperature.
Red. Leucocytes.
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
40000
30000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000

CHART I. — PNEUMONIA, SHOWING FALL BY CRISIS. — CASE 6.

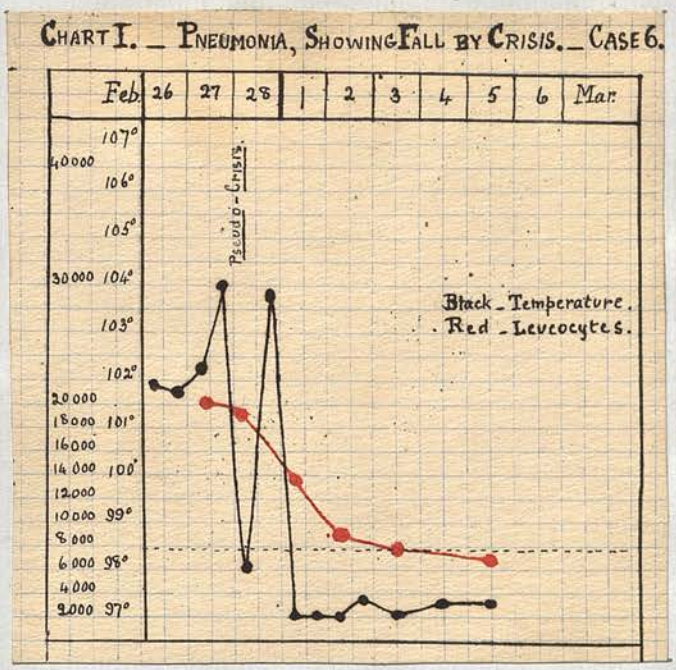
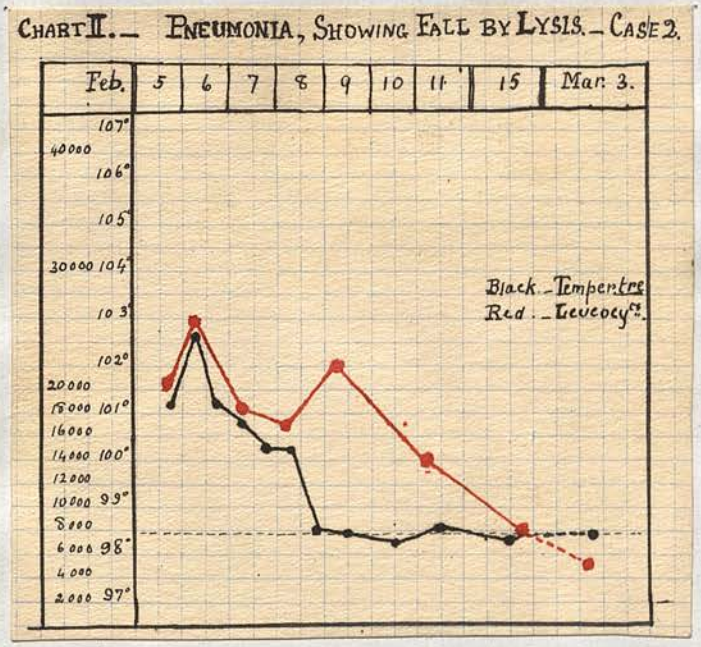


CHART II. — PNEUMONIA, SHOWING FALL BY LYSIS. — CASE 2.



If another acute inflammatory process be superadded to the primary disease it has the effect of causing the leucocyte curve to remain more or less highly elevated for a longer or shorter period according to the nature of the complicating affection.

See Chart IV.

As a rule slight oscillations of the temperature produce no effect on the leucocytosis. In the case of a pseudo-crisis the leucocyte count remains high. On the other hand, as will be noted more particularly below, a leucocyte pseudo-crisis may occur with the temperature remaining high.

That, in those cases where the temperature has come down to and remains at normal and where nevertheless resolution is delayed, leucocytosis is long continued, I cannot affirm. For instance in case 2 there was considerable delay in resolution, and the leucocytosis remained less than a week after the crisis.

3. Degree of Leucocytosis.

The degree of leucocytosis varies. It is as a rule considerable in acute pneumonia. My highest count was 54,000 in a case complicated with pleurisy. Still higher counts have been recorded. The period in the course of the affection at which the highest degree of leucocytosis is to be found varies : sometimes it occurs early in the process ; at other times just before the crisis.

I have found no direct connection to sub-

- sist between

sist between the height of the fever and the degree of the leucocytosis.

Neither was there found to be any direct connection between the severity of the attack and the degree of leucocytosis except that very mild cases are as a general rule associated with a slight leucocytosis and that there are certain severe and usually fatal cases which run their course without exhibiting any increase but rather showing a decrease in the number of white corpuscles.

What connection there exists between the extent of the consolidation and the degree of leucocytosis I shall have to discuss later, as also the reasons for the non-appearance of leucocytosis in certain cases, and in others the disappearance of a leucocytosis previously existing in the blood.

I shall now discuss what Sherrington in his paper on Inflammatory Leucocytosis terms the

C. Disturbance of the Numerical Ratios Normal between the Various Kinds of Haemic Leucocytes.

Much more interesting, far more constant, and I believe vastly more important both from a haematological and also from a purely clinical standpoint, than the consideration of variations in the gross number of leucocytes is the observation of the numerical ratios which the different forms of leucocytes bear to one another at different periods in the course - of the

of the pneumonic process ; and of equal importance is the estimation of the absolute number of each form found per unit volume of blood in the different phases of the affection.

From a haematological standpoint I divide all cases of croupous pneumoniainto two groups.

a. Cases occurring with leucocytosis.

b. Cases occurring without leucocytosis.

a. Cases occurring under the first head form the great majority of all cases of acute pneumonia and will be considered first. Three stages or phases of the leucocytosis will be described ; these may be conveniently termed :-

(1) Early Stage

(2) Later Stage

(3) Stage after Crisis

(1) Early Stage.- This stage begins soon after the initial rise of temperature. It lasts from a few hours to three or four days.

If the blood is examined at an early period in the course of the affection, e.g. the second day, it will usually be found that there is marked leucocytosis. On examinations of the blood films it will be found that the polynuclear cells are relatively to the other forms slightly increased. The large mononuclear cells are absolutely, and relatively to the lymphocytes very greatly increased. The latter are generally absolutely diminished. The eosinophilic cells are absent.

- To give

To give an example let us suppose that a healthy man has 7000 leucocytes per c.m.m.; he is seized with an attack of croupous pneumonia and early on the second day of the attack 20,000 leucocytes are counted in his blood. The relative percentage ratios of the various forms in a typical case might be represented as follows :-

	Before the attack	Second day
Polynuclear	72 %	80 %
L. Mono.& Transit.	5 %	12 %
Lymphocytes	20 %	8 %
Eosinophiles	3 %	0 %
	100 %	100 %

What strikes one most forcibly on examining a film preparation of the blood at this stage is the great relative increase of the large mononuclear group to the lymphocytes. The latter instead of being much more numerous than the other as in health are usually much fewer in number. As the disease progresses we find that the large mononuclear cells become diminished until they come to equal or nearly equal the lymphocytes in number. The polynuclear cells are proportionately augmented in numbers.

From a very early stage in the process the eosinophilic cells are diminished not only relatively but absolutely in the blood and the diminution of these cells contimues to the end of stage (2). Indeed it is rare to come across an eosinophilic cell - in the

in the blood film taken during the acute febrile period of croupous pneumonia. Plate I. Fig.1.is a photo-microgram representing a typical blood field in the early stage of croupous pneumonia.

Plate II. Fig. 1. is a coloured diagramatic representation of the blood at the same stage. Both figures show an increase of the large as compared with the small mononucleated cells and an absence of the eosinophiles. Chart V. is the result of the blood examination in case 17. The curve of the large mononucleated cells is seen indicating at first a high percentage of these cells which quickly falls until it closely approaches that of the small cells. The curve of the polynuclear cells shows a progressive increase in their relative percentage ratio. A high relative increase of the large mononuclear cells to the lymphocytes is, as far as my observations go, a characteristic feature of the blood at the commencement of all acute inflammatory conditions .

Chart VI. represents the same phenomena as occurring in a case of septic pneumonia following excision of portion of the tongue.

Chart VII. diagramatically shows the absolute count of the different forms in case 17. This chart is specially given to show the increase in the absolute number of the large mononuclear cells which so far from suffering a diminution are greatly increased at the commencement of the process and remain if anything, - slightly

slightly increased up to the termination - the average number of these cells being normally about 450 per c.m/m.. The circumstance, that the absolute number of these cells is usually increased in the common form of leucocytosis has never, so far as I know, been pointed out previously. The first stage is often so transitory in acute pneumonia, where the maximum intensity of the process quickly occurs, that it frequently passes unobserved. It is more in evidence in other inflammatory conditions where the progress of the affection is more gradual.

(2) Later stage.- There is no strict dividing line between this stage and that just described. It corresponds to the period of maximum increase of the polynuclear cells ; it is the stage of great relative diminution of both forms of mononuclear cells considered together as compared with the polynuclear cells. The latter cells sooner or later reach a high relative percentage. They generally come to number over 85 %, usually about 90 %, and twice in my observations reached the high figure of 95 % of all the haemic leucocytes. (Cases 12 & 17). The small and large cells in fairly equal proportions make up the remainder.

These relative percentage ratios are maintained with surprisingly little variation up to the critical fall of temperature notwithstanding frequently the occurrence of slight oscillations in the total number of leucocytes per unit vol. of blood.

- Plate I.

Plate I. Fig. 2. is from a case at the fifth day and shows great increase of the polynuclear cells.

Plate II. Fig. 2. also represents the same stage.

(3) Stage after the crisis.- With the occurrence of the critical fall of temperature a remarkable series of changes takes place in the relative percentages of the cells, and, what is of the greatest importance these alterations in the relative percentage ratios occur whether or not there coincidently occurs any appreciable diminution in the total number of leucocytes per unit of blood. If the blood is examined within a few hours of the crisis, it is found that there is a great reduction in the polynuclear cells, corresponding increase of the mononuclear, and perhaps the reappearance of a few eosinophiles.

Let us suppose the individual referred to above in stage (1) had a typical attack of croupous pneumonia, that his blood was examined on the eighth day of the affection and the leucocytes number-ed 22,000; in the afternoon of that day the crisis occurred. Suppose next morning it was found the leucocytes were slightly reduced, say 18,000 in number; changes very similar to the following would probably be revealed on examination of the blood films :-

	Stage 2 (8th day)	Stage 3 (9th day)
Polyn.	90 %	79 %
Large mono.	5 %	10 %
Small mono.	5 %	10 %
Eosinop.	0	1 %
	100	100

- On the

On the following day the polynuclear cells would be found to be still more decreased, the lymphocytes on the other hand still furtherincreased, and for the first time in the course of the affection these cells would outnumber the large mononucleated cells. In other words the relative increase of the large cells occurring at the crisis is transitory(sometimes it is not noticed to occur); the increase of the small mononucleated cells continuous and progressive. For clinical examples of these changes see especially cases 7, 8, 9, 12, and Charts VIII. and IX.

See also Plate I. Fig.3, which is from a film preparation taken one day after the crisis; also Plate II. Fig.3 which represents schematically the same set of changes.

A quick relative increase of the lymphocytes to the large mononucleated cells, especially when this change is associated with a speedy return of the eosinophiles is a favourable sign. It indicates a true crisis.

In the case of a lysis the same events occur but the return to normal is slower, the stage of increase in the large mononucleated cells being of relatively longer duration. The occurrence of the phenomenon which was pointed out by me in 1897 has been since corroborated by Türk. In these cases the reappearance of the eosinophiles is also later.

In cases terminating by crisis the last named cells are found to occur in something like their

- normal

normal relative proportion in from 1 to 6 days after the fall of the temperature. After slight attacks they seem to appear earlier than in cases where the patient was severely ill.

In from three days to a week on an average after the occurrence of the crisis the relative numerical ratios of the different cells have resumed something like the condition found in health.

A pseudo-crisis is attended with but little change in the relative proportions of the cells. Case 6, Chart X. is an apparent exception to this in so far that there was a decided change occurring after the first fall of temperature. At the time one thought a true crisis had occurred both from a clinical point of view (the pulse, respirations, and general symptoms indicated it) and also from the examination of the blood. At night however the temperature went up again and there was every appearance of the occurrence of a relapse. Next morning the temperature again fell to normal and theblood examination this time revealed an unmistakeable "leucocyte-ratio" crisis. The temperature continued subnormal.

A decided fall in the total number of leucocytes during the acute attack as in cases 3 and 4 (Charts XI. and XII.) is accompanied by a considerable decrease in the percentage ratio of the polynuclear cells, and a relative increase of the mononuclear cells. If instead of the percentage ratio the absolute count of the cells is taken, the fall in the number of the polynuclear cells and the comparative

- steadiness

steadiness of the other forms is more strikingly seen .(Chart XIII and XIV)

This condition is differentiated from what occurs at the crisis by the fact that the tempara - ture still remains high, that there is a continuous great relative increase of the large to the small mononucleated cells, and the eosinophilic cells remain absolute.

A continued relative increase of the large mononuclear cells particularly when accompanied by a continued absence of eosinophiles, and especially in those cases where the temperature has fallen to some extent, is a condition very often associated with the superaddition of an acute inflammatory complication - see case 13, 14, 15, Chart XV. The microscopic field in these cases bears a striking resemblance to that seen in Stage (1)

In chart XVI I have constructedwhat I believe to be a typical diagramatic representation of the leucocyte variation in croupous pneumonia. But it must be borne in mind that just as in pneumonia scarcely two cases are alike in their clinical signs and symptoms, so we can hardly expect to find the blood condition to be exactly similar in two cases. Clinically however there are described certain classical signs and symptoms in croupous pneumonia and these ~~ø~~ occurring in a definite order, and so therefore after a similar manner it may be permissible to give a typical schematic representation of the blood ex-

- amination

amination in this affection -

(1) Cases occurring without leucocytosis.

The absence of leucocytosis was noted in three cases all of which terminated fatally .- In all the cases there was found to be present a remarkable change in the character of the white corpuscles in the blood - I have already alluded to two cases of pneumonia in which there was a temporary fall in the number of leucocytes. In both of these the leucocytes reappeared before the crisis and the patient recovered. In the cases I now describe the hypoleucocytosis remained till death. In the cases which recovered the fall in the number of leucocytes chiefly affected the polynuclear variety, and this is true also of the fatal cases. But this was not all, for in each of the cases there were present a large percentage of cells not found in the normal blood. For instance, in case 22 there were present on first examination 4400 corpuscles in the cubic millimetre and of these 35% were ordinary polynuclear cells, fourteen hours afterwards, and seven hours before the death of the patient, scarcely a typical polynuclear cell with fragmented nucleus was to be found in the film preparations. ~~6%~~ Six percent of the cells present were lymphocytes; types of the remaining cells are figured in PlateII. Fig.4,; these were drawn accurately from cells in the film preparations. Cell b is a large mononuclear cell; cell c is a transitional cell in which there are to be seen a few sparsely scattered fine oxyphilic granu-

- lations

lations in the protoplasm. It is a typical transitional white corpuscle of Ehrlich. The remaining types of white cells are finely granular oxyphiles so far as their protoplasm is concerned. Of these cell d is a myelocyte whose nucleus is somewhat indented. In e and f we have the nucleus still further condensed and fragmented. These latter cells are typical finely granular oxyphile cells in everything but size, being much larger than the ordinary cell. These cells are known as polynuclear myelocytes. Although in this case at the last blood examination 94% of the leucocytes present belonged to the large mononuclear and myelocyte groups, the latter being about five times as numerous as the former, yet the great percentage of cells found in the consolidated portion of lung was apparently made up of typical polynuclear leucocytes. Plate I. Fig.4 is a photo-micrograph taken from a blood-film from case 23. In this case and in case 21 the blood condition was very similar but there were present a relatively larger number of the typical mononuclear myelocytes than in case 22 ; in both cases the myelocytes constituted about 85% of all the leucocytes present :

(c) Resumé of above changes.

I shall now give a resumé of the behaviour of the different forms of white corpuscles in the leucocytosis of pneumonia and compare my results with the observations of others.

(1) Polynuclear Leucocytes.- The number of these is usually absolutely ~~and~~ and relatively greatly increased. - This

This is universally admitted. On the other hand in cases of hypoleucocytosis in pneumonia, the diminution chiefly affeats these cells. Biegański has observed lately lethal ending cases of pneumonia where a diminution of these cells occurred. With the fall in the total number of leucocytes at the close of the leucocytosis there occurs a relatively quicker fall in the curve of the polynuclear cells, owing to the increase which occurs in the lymphocytes. This is in accordance with the conclusions of Stiénon , but does not correspond with the diagram which he gives in his monograph.

(2) Large Mononuclear and Transitional Leucocytes.-

Ehrlich says that these do not correspond to the chemotactic stimuli which provokes an ordinary leucocytosis. My opinion is diametrically opposed to this view. It is true that the relative count of these cells during the acme of the process is usually not much raised nor lowered. I have however observed at the commencement and end of an attack of pneumonia a considerable relative increase of these cells. Biegański observed an increase of these cells to 10% occurring after the crisis. Later Türk and Durham (1898) noted an increase of these cells in cases where the fall of the temperature was somewhat protracted.

But further it will be noted , if the absolute count of these cells is made, that their actual numbers are increases usually from 1½ - 5 times the average number. These cells also appear to be affected by slight chemotactic influences in nearly equal

- degree

degree to chemotaxis of greater intensity and being more susceptible to weak chemotaxis than the polynuclear leucocytes, their relative percentage ratio is consequently often found increased both at the beginning and end of inflammatory processes especially when the commencement and termination of such processes is not very abrupt.

(3) Lymphocytes. Observers are agreed that the relative percentage ratio of these cells is greatly decreased in the acute stage. Their absolute count is then also often diminished.

At the crisis some observers, especially Stiénon, note a relative increase of these cells above the normal. Neither Türk nor I have found that this is usually the case. The absolute count of these cells is however generally increased at this time.

(4) Eosinophiles.- These are both relatively and absolutely greatly diminished during the acute stage. They may appear in diminished numbers shortly before the crisis. Frequently and especially in less severe cases they appear in augmented number after the critical fall of temperature.

(5) Abnormal leucocytes. (a) Myelocytes.- I found these present in great numbers (30-85%) in certain lethal ending cases occurring with a diminished leucocyte count. Türk found towards the crisis in severe cases of pneumonia occurring with leucocytosis a small percentage of "neutrophile mononuclear cells"; sometimes these however were present to so many as 10% of the total number of haemic leucocytes. They corresponded in size as a rule to the common polynuclear neutrophiles, but occasional larger individuals were

were present and not to be distinguished from myelocytes. I have seen only occasional myelocytes present in the blood in ordinary cases of pneumonia.

(b)"Reizungsformen".- These have lately been described by Türk as occurring in pneumonia in similar conditions and in company with the last mentioned cells. They are non-granular mononucleated cells which stain in a peculiar way with the tri-acid solution. If present in my cases they have been included under the non-granular cells.

Plate I

Fig 1.

Fig. 2.

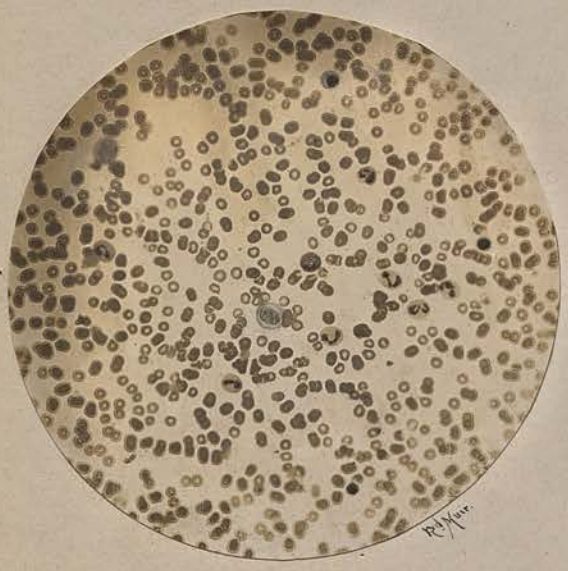


Fig 3

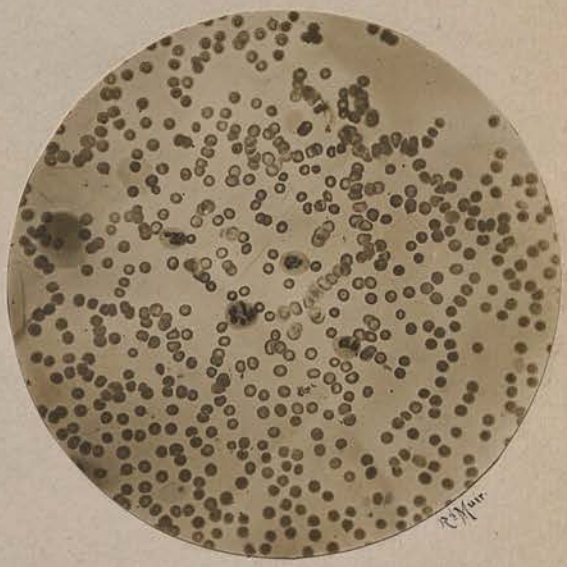


Fig 4

Plate II

Fig. 1.

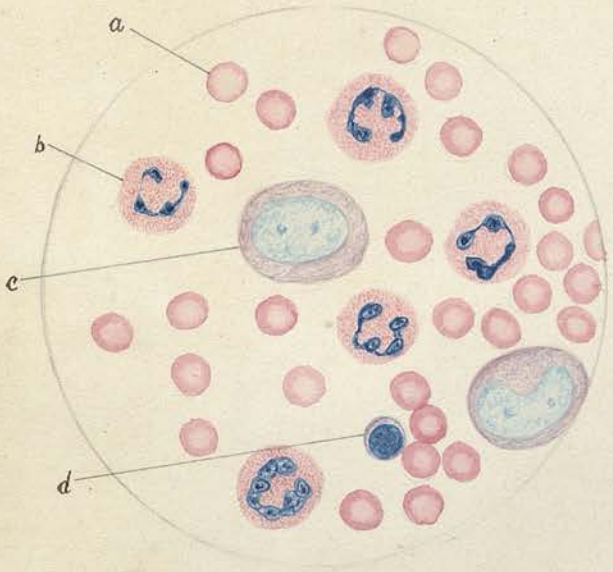


Fig. 2.

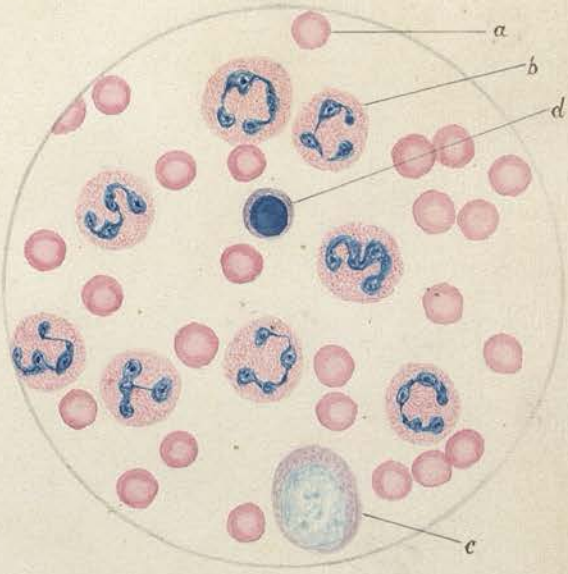


Fig. 3.

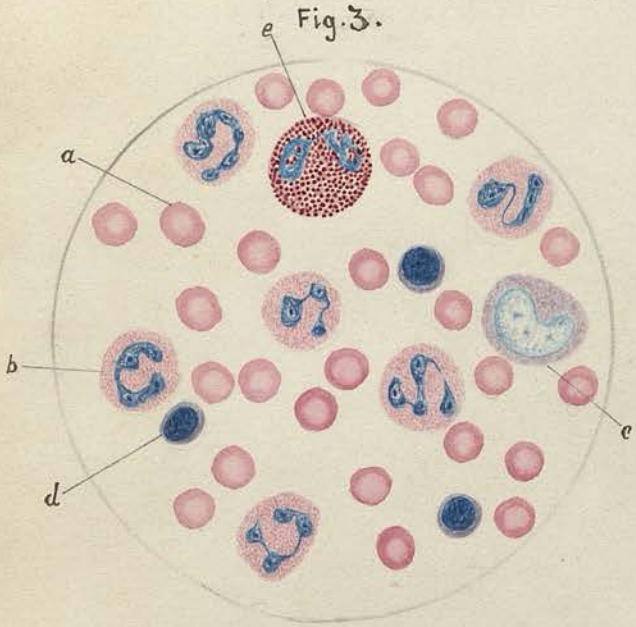
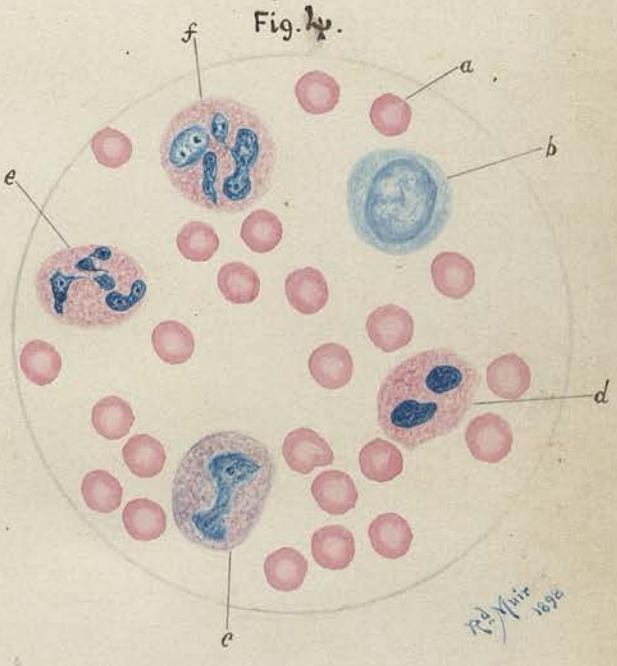
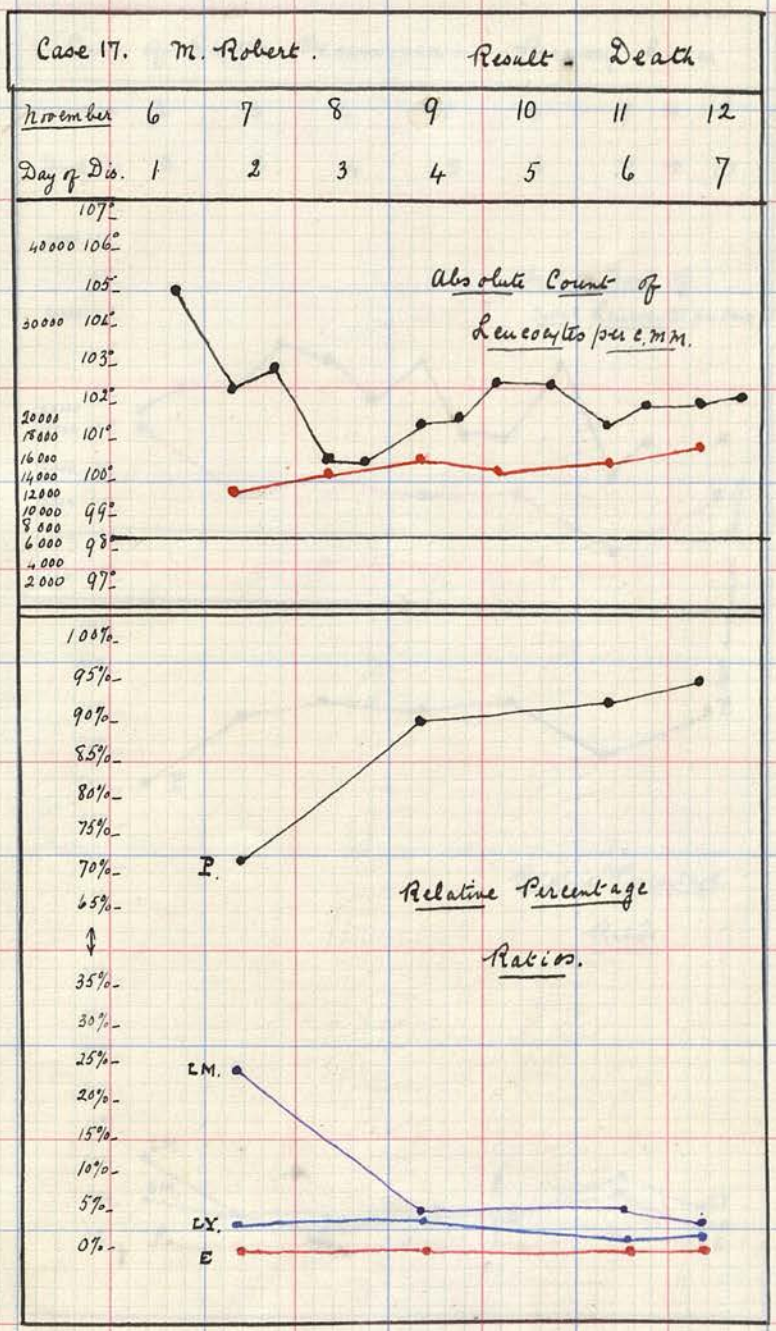


Fig. 4.



R.d. Muir 1896

Chart V



Black - Temperature.
Red - Leucocytes. (Total Count).

Black - Polynuclear.
Violet - Large Mononuclear
Blue - Lymphocytes.
Red - Eos in ophiles.

Chart VI

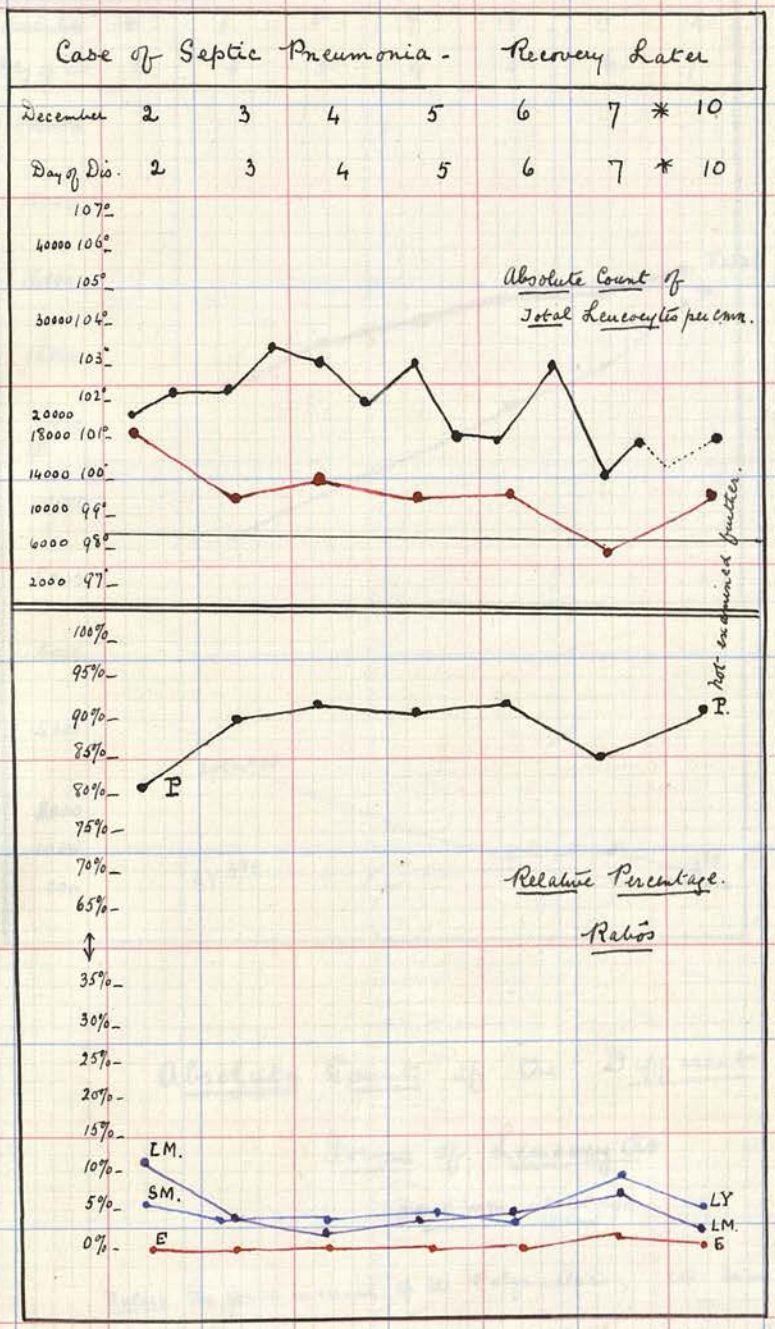
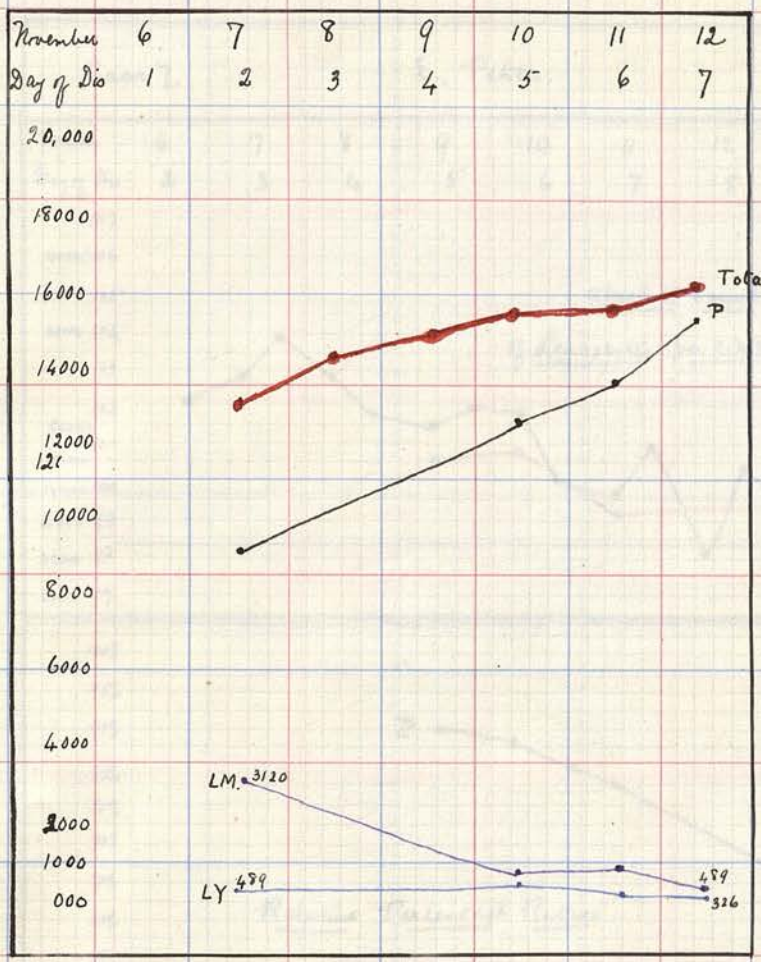

Case of Septic Pneumonia - Recovery Later
December 2 3 4 5 6 7 * 10
Day of Dis. 2 3 4 5 6 7 * 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
40000
30000
20000
18000
14000
10000
6000
2000
Absolute Count of Total Leucocytes per cmm.
Black - Temperature
Red - Leucocytes.
Not examined fractions.
100%
95%
90%
85%
80%
75%
70%
65%
35%
30%
25%
20%
15%
10%
5%
0%
P.
P
Relative Percentage. Ratios
Black - Polymuclear
Violet - Large Mono.
Blue - Lymphs.
Red - Eosinophs.
LM.
SM.
E
LY
LM.
E

Chart VII

Case 17.



Averages in Health per c.mm.

Red - Total Leucocytes --7000.

Black Polynuclear ---4900

Violet Large Mononc. & Transit ---420.

Blue - Lymphocytes ---1400

Absolute Count of the Different Forms of Leucocytes per c.mm. of blood.

Notice the great increase of the Polynuclear; the increase of the L. Mononuclear and Transitional; and the Decrease of the Lymphocytes.

Chart VIII

Case 7. E., Peter. Result: Recovery.

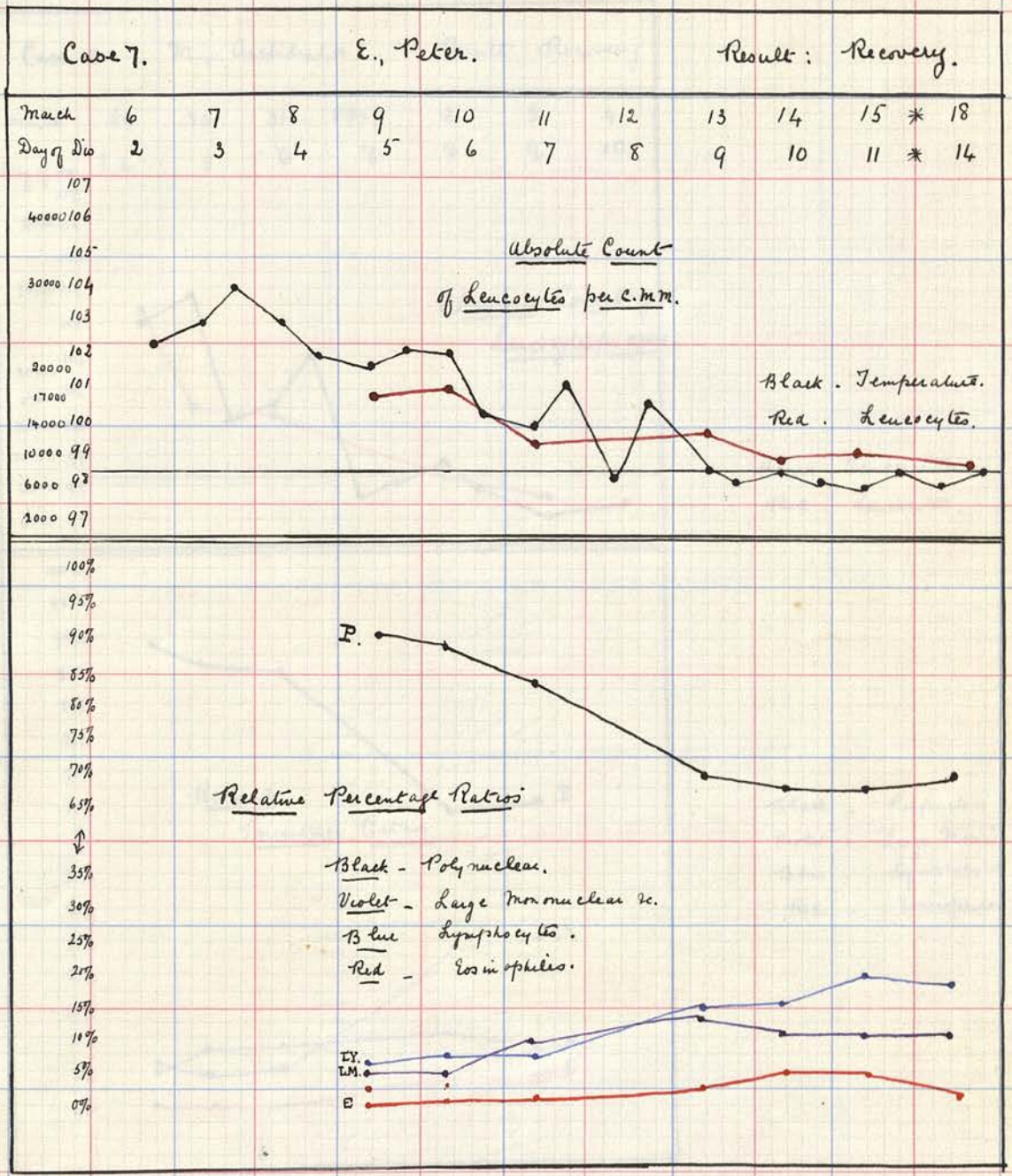


Chart IX

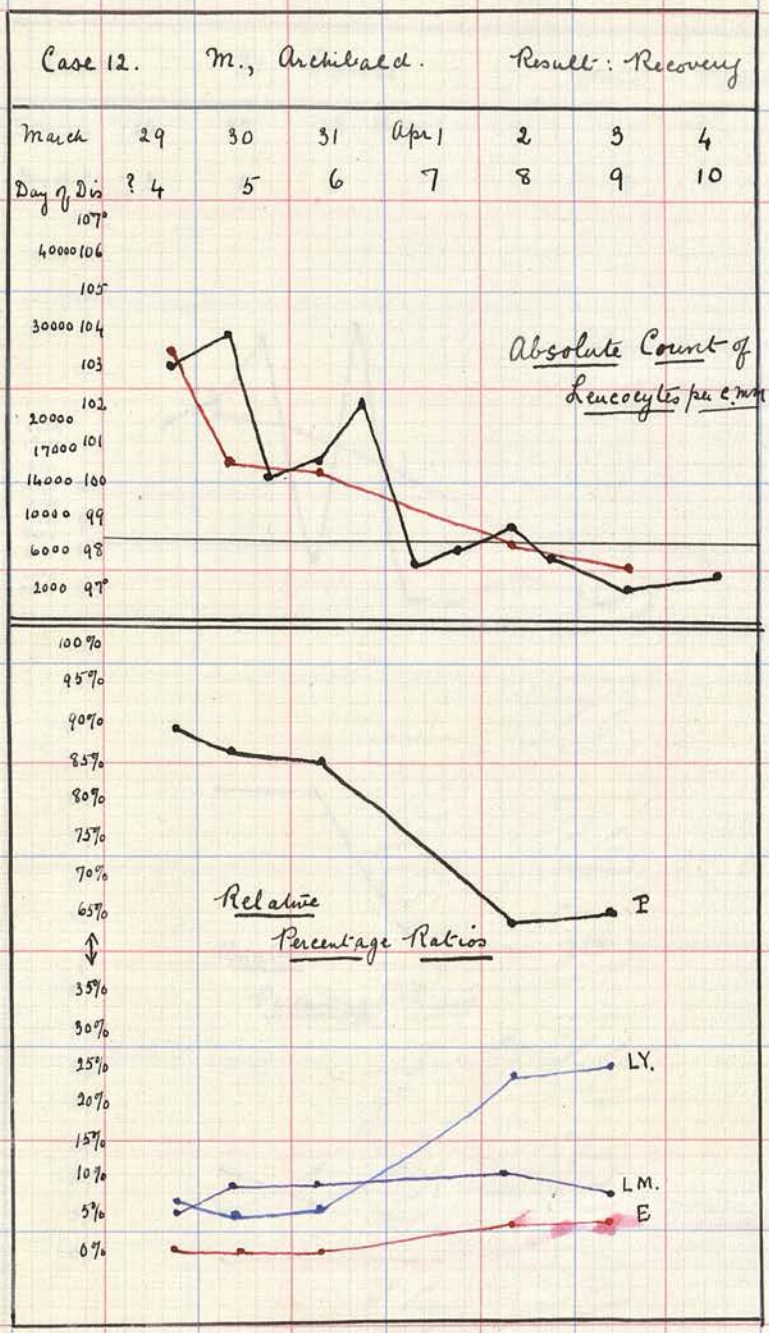

Case 12. M., Archibald. Result: Recovery
March 29 30 31 Apr 1 2 3 4
Day of Dis ? 4 5 6 7 8 9 10
107°
40000 106
105
30000 104
103
102
20000
17000 101
14000 100
10000 99
6000 98
2000 97°
Absolute Count of Leucocytes per c.mm.
Black - Temperature
Red - Leucocytes.
100%
95%
90%
85%
80%
75%
70%
65%
35%
30%
25%
20%
15%
10%
5%
0%
Relative Percentage Ratios
P
LY.
LM.
E
Black - Polynuclear
Violet - Large Mono^s.
Blue - Lymphocytes.
Red - Eosinophiles.

Chart X

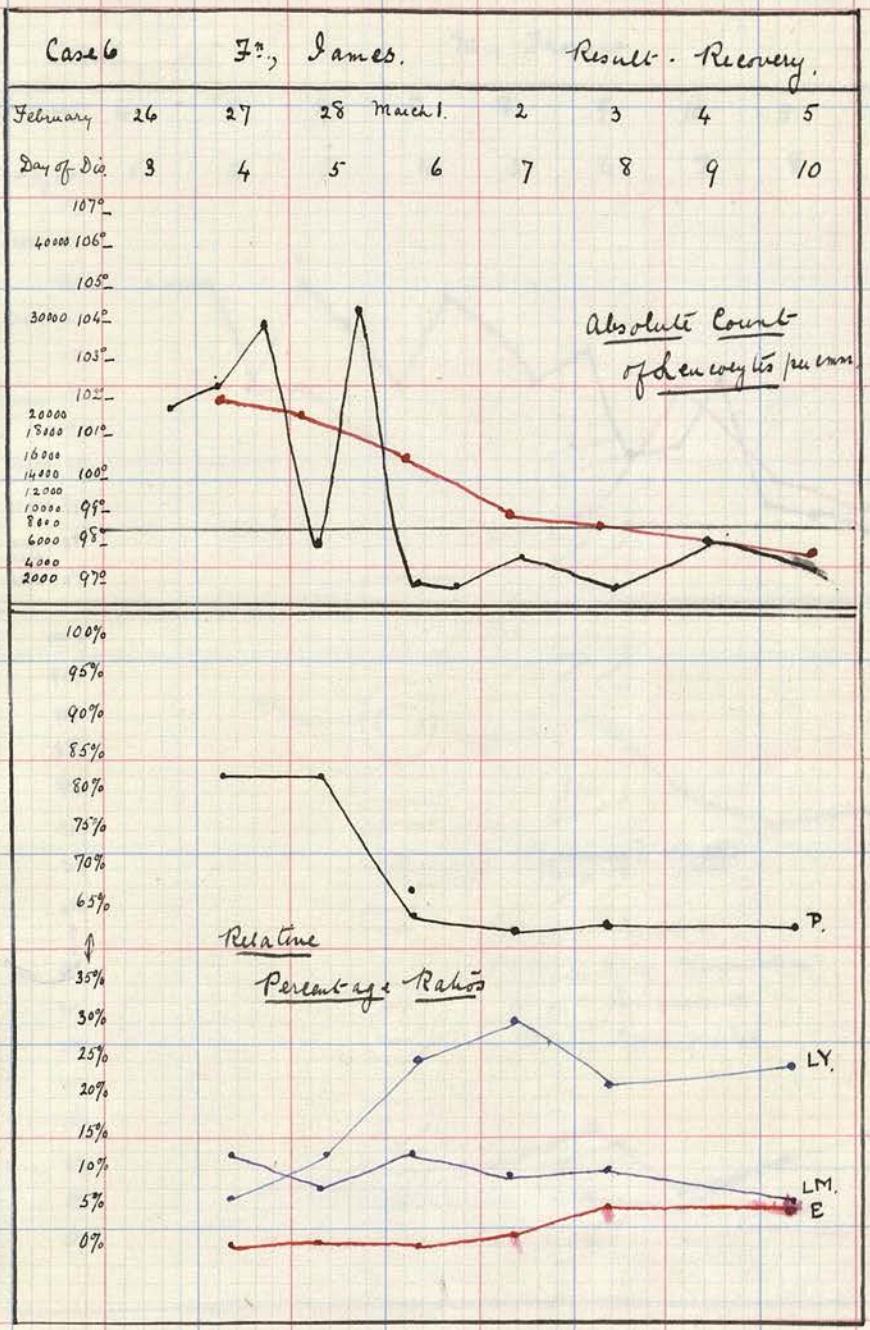

Case 6
Fr., James.
Result - Recovery.
February 26 27 28 March 1. 2 3 4 5
Day of Dis. 3 4 5 6 7 8 9 10
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
40000
30000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
Absolute Count of Leucocytes per cmm.
Black - Temperature.
Red - Total Leucos.
100%
95%
90%
85%
80%
75%
70%
65%
35%
30%
25%
20%
15%
10%
5%
0%
Relative Percentage Ratios
P.
LY.
LM.
E
Black - Polymuclears.
Violet - Large Mono's.
Blue - Lymphocytes.
Red - Eosinophiles.

Chart XI

Case 1. M., Thomas Result: Recovery.

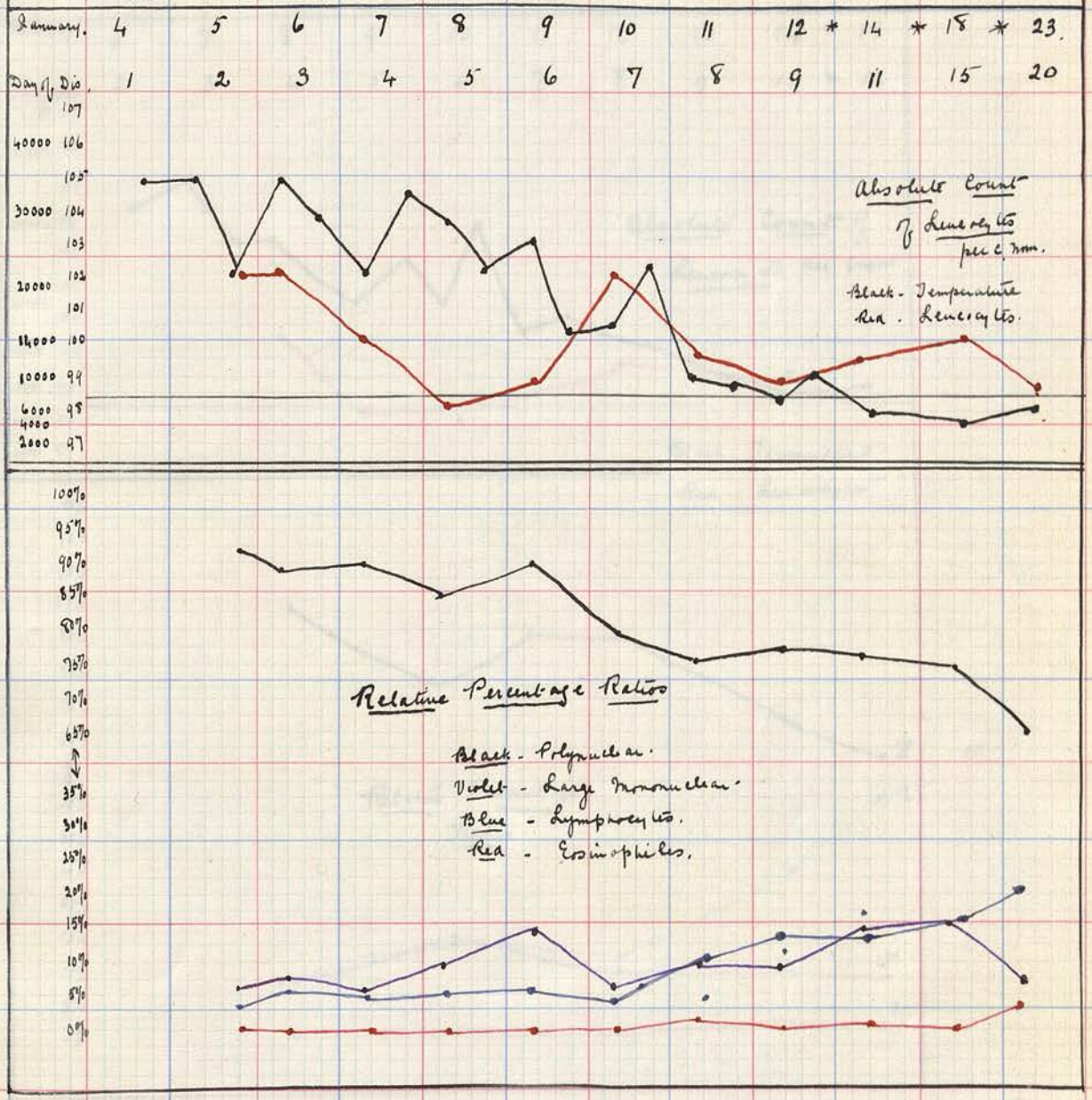


Chart XII

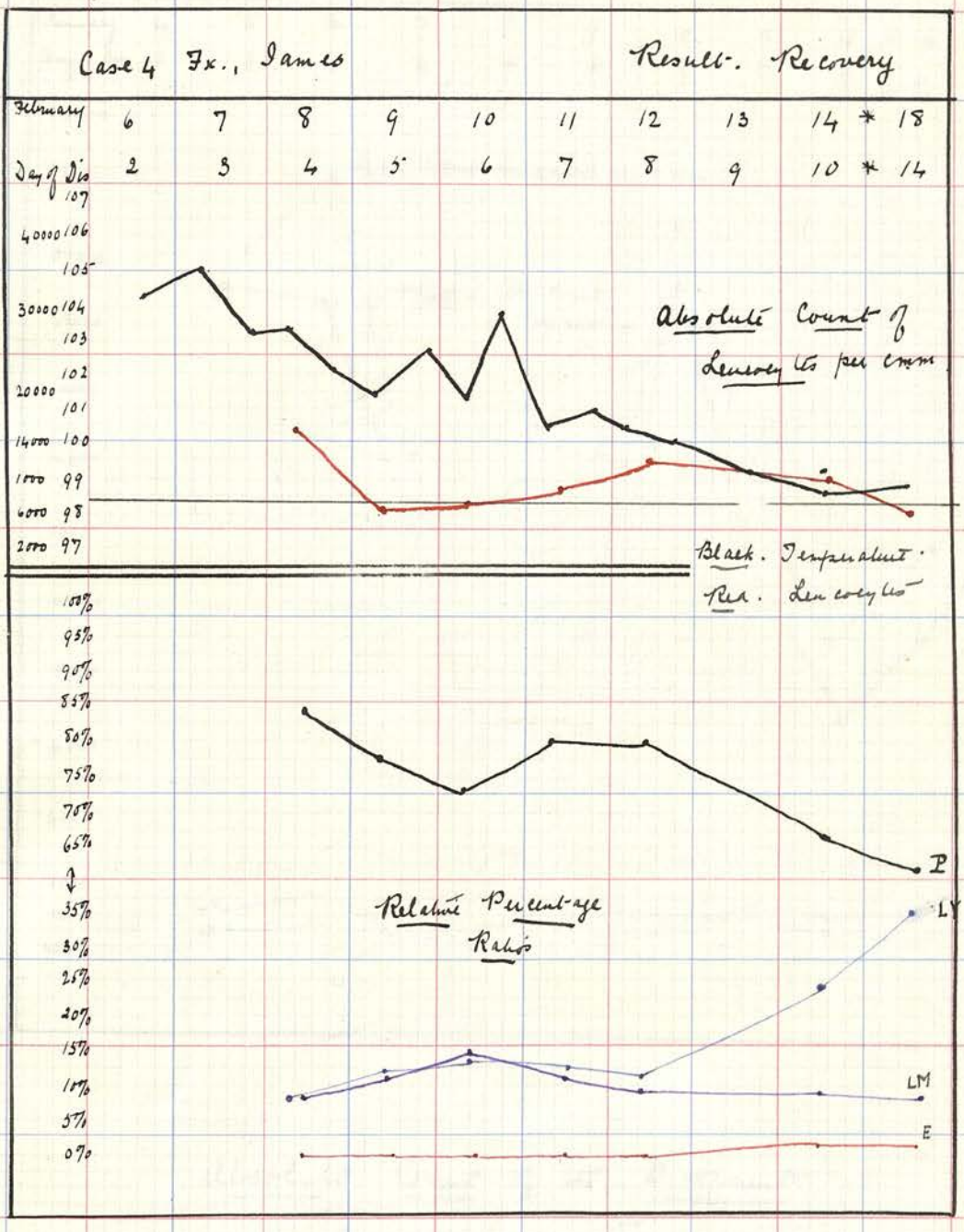
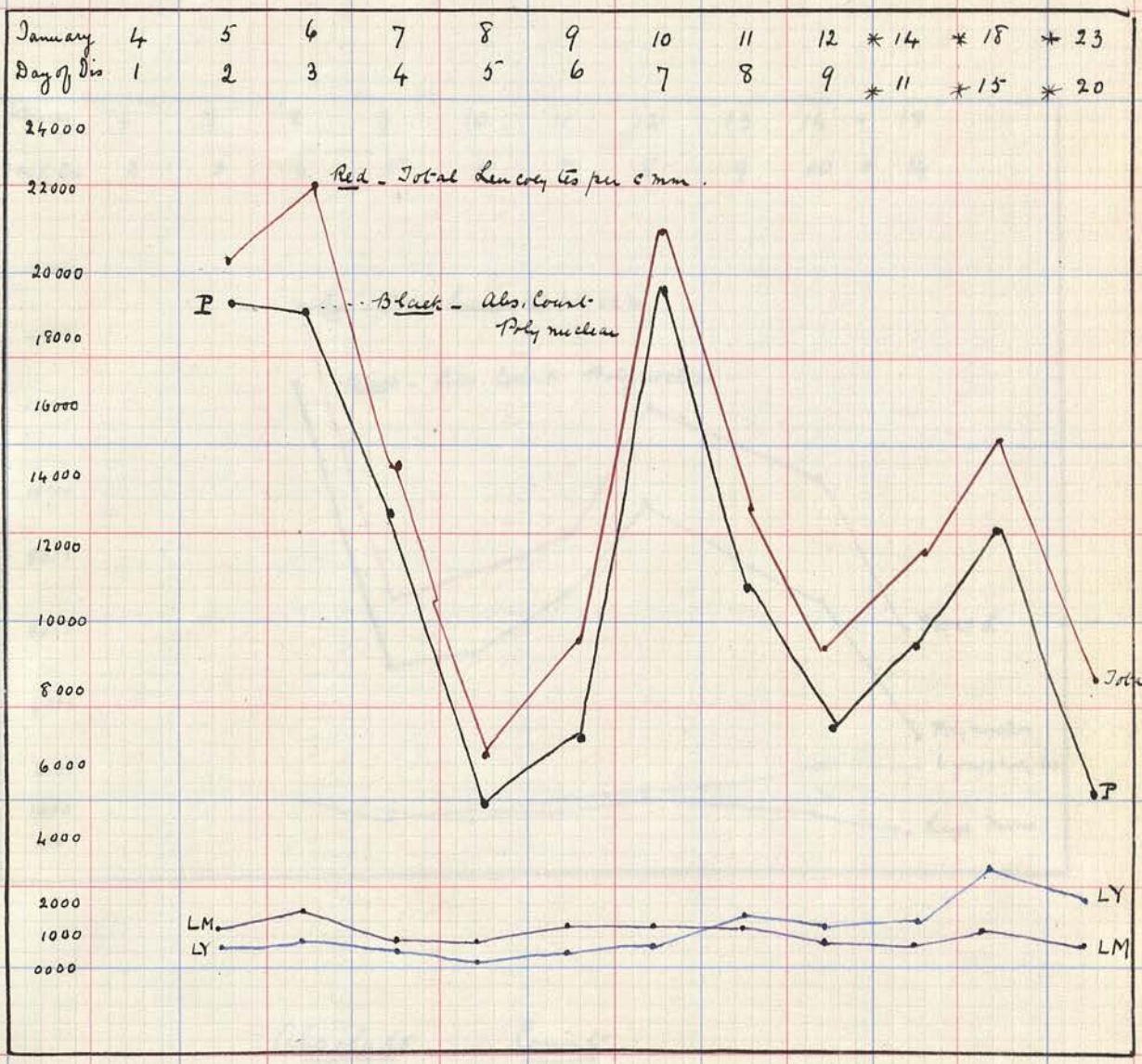

Case 4 Fx., James
Result. Recovery
February 6 7 8 9 10 11 12 13 14 * 18
Day of Dis 2 3 4 5 6 7 8 9 10 * 14
107
40000 106
105
30000 104
103
102
20000
101
14000 100
1000 99
6000 98
2000 97
Absolute Count of Leucocytes per cmm.
Black. Temperature.
Red. Leucocytes
150%
95%
90%
85%
80%
75%
70%
65%
35%
30%
25%
20%
15%
10%
5%
0%
Relative Percentage Ratio
P
LY
LM
E

Chart XIII

Case 1.



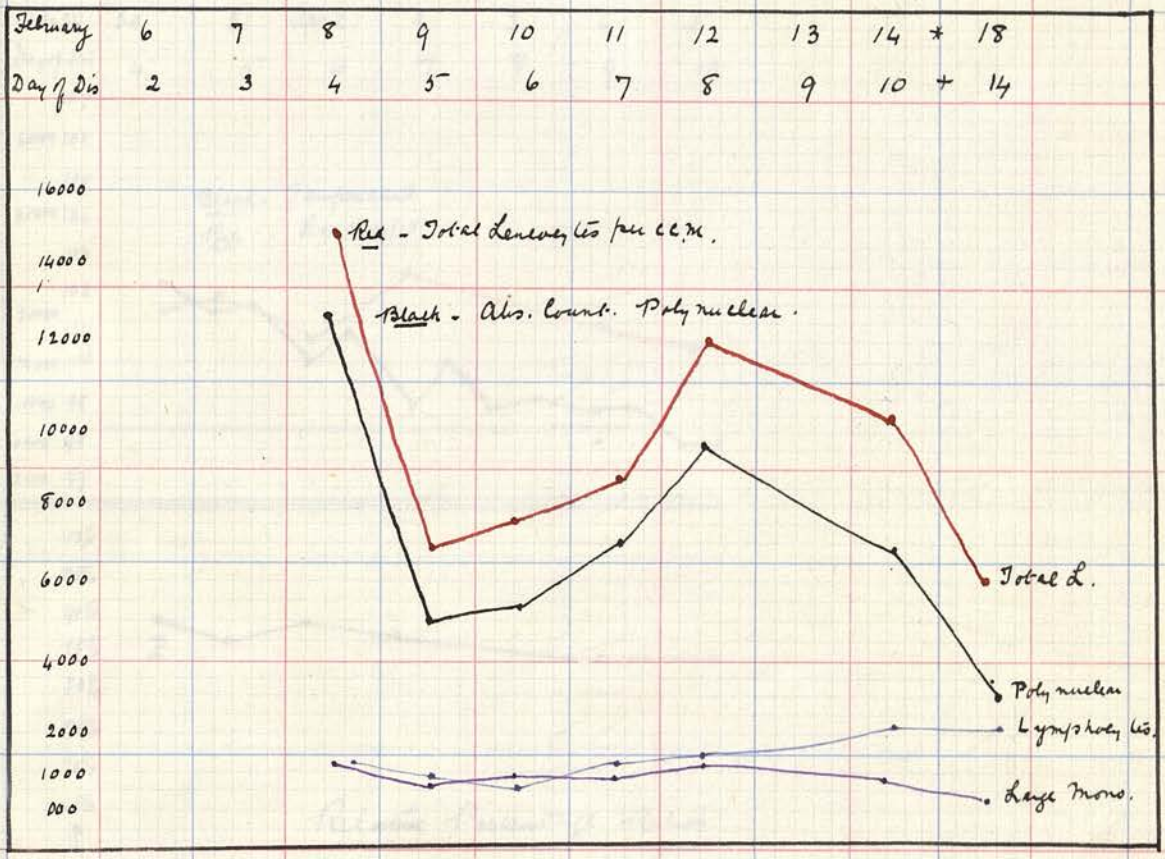
Absolute Count of the Different Forms of Leucocytes per c.mm of blood.

Notice (1) that in the "Leucocyte Pseudo-Crisis" the fall chiefly affects the Polynuclear Form.

(2) Increased absolute count of the Large Mononuclear and Transitional Forms during the Leucocytosis.

Chart XIV

Case 4



Absolute Count

of the

Different Forms

of Leucocytes per c.m.m. of blood

Cf. Chart XIII

Chart XV

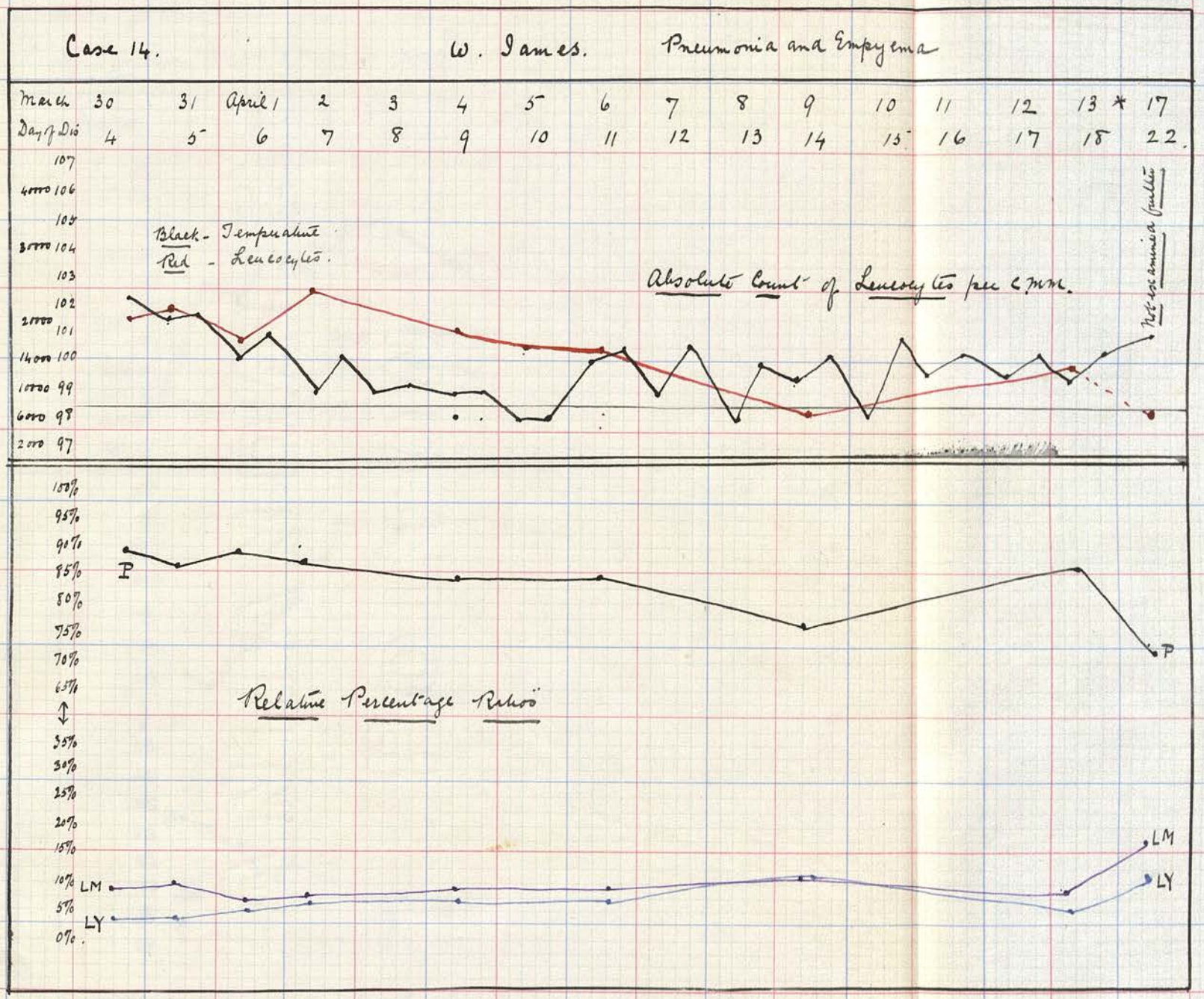
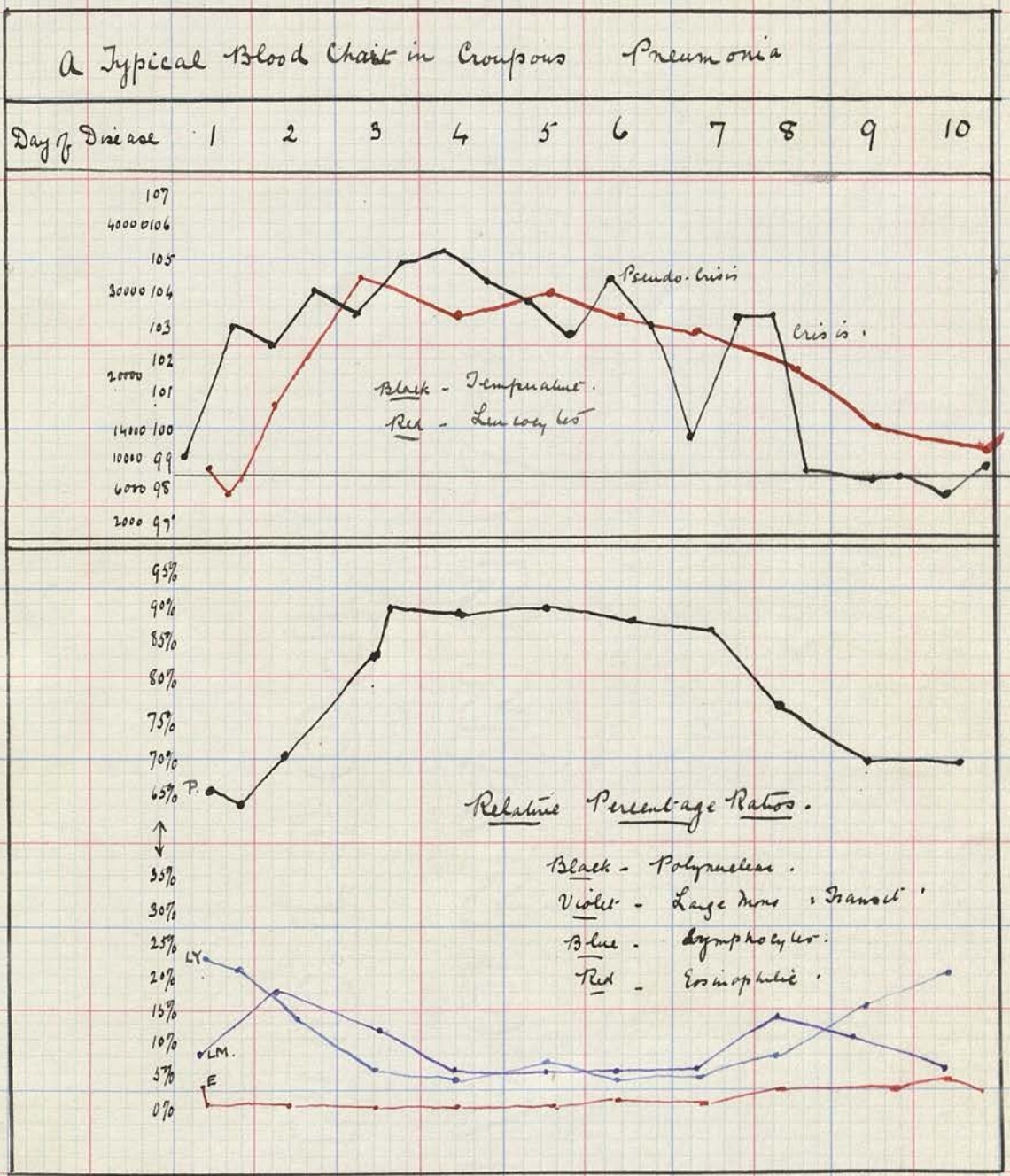

Case 14.
W. James.
Pneumonia and Empyema
March 30 31 April 1 2 3 4 5 6 7 8 9 10 11 12 13 * 17
Day of Dis 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 22
Black - Temperature
Red - Leucocytes.
Absolute Count of Leucocytes per c.mm.
Polymorphonuclear (pallid)
P
Relative Percentage Ratio
LM
LY

Chart XVI


A Typical Blood Chart in Croupous Pneumonia
Day of Disease
1
2
3
4
5
6
7
8
9
10
107
106
105
104
103
102
101
100
99
98
97°
40000
30000
20000
14000
10000
6000
2000
Pseudo-crisis
Crisis.
Black - Temperature.
Red - Leucocytes
95%
90%
85%
80%
75%
70%
65%
P.
35%
30%
25%
20%
15%
10%
5%
0%
LY.
LM.
E
Relative Percentage Ratios.
Black - Polynuclear.
Violet - Large mono: Transit.
Blue - Lymphocytes.
Red - Eosinophiles.

Chapter XI.

Conclusions regarding the occurrence of the Leucocytosis in Croupous Pneumonia

It is difficult in the midst of confusing and more or less contradictory theories and experiments to arrive at any definite conclusion regarding this matter.

In considering the subject it is necessary to bear in mind two essential features of the affection :-

1. Febrile symptoms due to the specific action of the pneumotoxin or pneumotoxins.
2. Inflammatory exudation.

It is extremely doubtful if the action of the pneumonic poison directly produces leucocytosis or at allevents any high degree of leucocytosis. Rabbits inoculated with Fraenkel's diplococci die of acute septicaemia and there is observed no leucocytosis. Further that no specific action in this respect can be attributed to the pneumococei as compared with other organisms is shown for instance by the fact that septic pneumonia often presents as high a degree of leucocytosis as that occurring in true croupous pneumonia. Sherrington in his experimental work has definitely proved that an acute inflammatory leucocytosis, similar to what occurs in pneumonia, can originate altogether apart from the action of organisms.

The occurrence of the leucocytosis in pneumonia and the inflammatory exudation are closely connected as regards their origin : In other words the

- general

general and local leucocytosis are due to the same cause. The action of the organisms on the lung tissue produces irritation products ; these cause a local leucocytosis due to the action of a local chemotaxis, but at the same time these irritants find their way into the blood stream and cause a general or haemic leucocytosis occasioned by the action of a general or haemic chemotaxis.

The degree of the general leucocytosis in pneumonia is therefore dependent on (1) the absorption into the blood stream of positively acting chemotactic irritants produced by the pneumococci.

(2) It is further dependent on the amount of the exudation. The inflammatory exudation in pneumonia is exceedingly rich in haemic leucocytes ; the number of leucocytes present in the fluid scraping of the consolidated portion of a lung in one case of pneumonia showed nearly 500,000 cells (mostly leucocytes) per c.m/m. The great loss in number of the haemic leucocytes due to emigration into the lung alveoli must accordingly be taken into consideration. It may be inferred from this that there may be a great increase in the inflow of leucocytes into the blood of the general circulation, though on account of extensive emigration no increase or only slight increase in their numbers is observable in the blood.

(3) The degree of leucocytosis is dependent on the nature of the infection and the resisting power of the individual. Climically in some cases it is noted that there is a great amount of consolidation and slight general symptoms ; in other cases

- the convers

converse is true. Otherwise stated in one class of cases the local action of the pneumococcus is the predominating feature ; in another class the general toxic effect is infinitely greater as compared to the local effect ; in another class of cases large extent of consolidation is accompanied by general symptoms of marked severity. These facts must be taken into consideration in seeking for an explanation of the occurrence of the leucocytosis and its degree. In severe cases owing to the virulence of the toxins ~~in~~ circulating in the blood, compared with the weak resisting power of the individual, and perhaps an impoverished blood supply to the leucocyte producing centre, there is no output of fresh leucocytes in corresponding ratio to the number of those lost from the blood stream.

(4) The amount of leucocytic destruction :- Although Löwit's statements regarding the amount of leucocytic destruction are probably erroneous, yet disintegration of the white cells in an increased rate most probably takes place in the internal organs in leucocytosis. Muir has lately (1898) corroborated this so far as concerns the spleen.

These points must be taken into consideration in endeavouring to understand the series of changes occurring in the white corpuscles of the blood in pneumonia.

(1) In the early stage the large mononuclear group are increased because they respond to slight chemotactic stimuli. Further they do not emigrate to such an extent as the polynuclear. The lymph-

-ocytes

ocytes do not partake, at least to any appreciable extent in the leucocytic process, consequently they are found relatively decreased. Their absolute decrease often seen may be explained by (1) destruction, (2) arrest in capillaries of internal organs such as occurs in injection leucocytosis but to a slighter degree than the large mononuclear or polynuclear leucocytes, and (3) exudation. The polynuclear cells are attracted from the bone marrow in increased numbers, but at first owing to rapid emigration out of the blood stream do not attain their full numbers.

(2) In the second stage the lymphocytes are still much decreased ; the large mononucleated and transitional group become relatively to the polynuclear diminished, on account of the large further increased flow of the latter cells from the bone-marrow into the blood stream, and also because, according to Ehrlich, the polynuclear cells owe their origin in small part to the transitional cells.

(3) In the stage after the crisis the large mononuclear cells are often to be found again relatively increased because they are susceptible to slighter chemotactic forces than the polynuclear and perhaps because there is an arrest in a great measure of their development into the polynuclear corpuscles. The eosinophilic cells which have been absent due probably to negative chemotaxis are to be found in considerable numbers after the crisis, because according to Ehrlich the products of the disintegration of tissues exert a positive chemotactic influence on them.

(4)

(4) Cases without leucocytosis.-

The most likely explanation of the presence of myelocytes in lethal ending cases is as follows :- The chemotactic force is very strong and has already drawn all the polynuclear reserves out of the bone marrow, the"reaction" of the individual is feeble and no new cells are produced to satisfy the strong chemotaxis, so the marrow cells themselves are drawn in by the attracting force, some of them, the more readily to pass into the blood stream, assume a polynuclear form.

In other cases a quick and decided but transitory fall of the leucocyte count, and especially of the polynuclear cells, during the acute attack is to be explained as due to a sudden increased exudation into the lung, which the haemic leucocytosis is not capable of meeting, or a temporary failure in its producing power.

Chapter XII.

Clinical Importance of the Blood Examination in Acute Pneumonia.

1. In Diagnosis.

From a diagnostic point of view the examination of the blood is often of the greatest importance. At an early stage where the history and symptoms would indicate croupous pneumonia but physical signs are not present, the occurrence of a leucocytosisespecially of high degree (say above 15,000) would be greatly in favour of pneumonia.

On the other hand if, some hours after the occurrence of a rigor, the blood of the patient is examined, and there is found to be no leucocytosis, and further ~~that~~ they lymphocytes are not relatively decreased in number as compared with the large mononuclear group, and especially if eosinophilic cells are present, it may be definitely asserted that no acute inflammatory process of any extent, and therefore no pneumonia, is present.

Pneumonia may thus be diagnosed from, more especially, typhoid, influenza, and acute phthisis.

In connection with the serum diagnosis of typhoid it is often useful. To cite a case : A patient with indefinite history, high temperature, physical signs of bronchitis and impaired resonance at the base of one of his lungs was supposed to be suffering from

-pneumonia

pneumonia. The blood examination showed 7000 leucocytes per c.m/m. On film examination the polynuclear, large mononuclear, and lymphocytes appeared in fairly normal proportion, the lymphocytes greatly surpassing the large mononuclear cells in number. Pneumonia was therefore excluded. The serum test showed a well marked reaction ; and the case finally turned out to be a typical one of typhoid fever.

The occurrence of leucocytosis complicating typhoid fever indicates the occurrence of an acute inflammatory complication, possibly pneumonia.

By the blood examination we may accordingly now be able to more readily differentiate between typhoid fever, typhoid fever complicated with pneumonia, and typhoidal pneumonia.

I have already referred to the fact that a tardy fall in the total number of leucocytes especially when associated with continued relative increase of the large mononuclear cells, occurring towards the end of a pneumonic attack, may lead one to suspect the occurrence of a secondary acute inflammatory complication.

By the blood examination alone a true lobar pneumonia (due to Fraenkel's pneumococci) cannot well be separated from a septic pneumonia. In the case of the latter affection, however, there is usually greater variation both in the total number and relative percentage ratios of the different forms of cells per c.m/m. of blood.

2. In Prognosis.

From this point of view the blood examination is in most cases of less value. The following conclusions may however be arrived at :-

1. The absence of a leucocytosis in a pronounced case of pneumonia is an extremely unfavourable symptom, especially where the examination of the blood film shows the presence of a high percentage of myelocytes. (cf. Engel's conclusions in diphtheria).

2. On the other hand the presence of a leucocytosis does not necessarily indicate that the affection will pursue a favourable course, nor that the patient is not liable to suffer from one of the many complications of the disease (e.g.pericarditis, empyema etc.).

3. In Treatment.

Experimentally it has been stated by various observers (more especially Jacob) that the artificial raising of leucocytosis in animals has conferred a certain degree of immunity in cases of inoculation with various bacteria. Loewy and Richter have lately (1898) gone carefully into this question and stated that in their observations when the remedy which provoked the leucocytosis was injected after the infection had already been introduced it never produced a curative result, at the most in this stage only a lengthening of life was afforded. Further they say that as yet we have got no drug which can be relied on to produce a high degree of leucocytosis. Their conclusions would indicate

cate the futility for the present of attempting clinically to treat pneumonia or other acute diseases along these lines.

The most that we can expect the examination of the leucocytes of the blood to help us therapeutically in such cases is as (1) an aid to the diagnosis of the affection, and (2) an indication of the severity of the case, so that early measures may be taken to strengthen the patient's resisting power where such shows from the blood side signs of failure.

P A R T III.

General Remarks as to the value of the Examination of the Haemic Leucocytes.

Chapter XIII.

Concluding Remarks on Leucocytosis..

In the recent works of v. Limbeck, Schmalz, Cabot, Coles, and Türk there are to be found detailed accounts as to the value of the examination of the haemic leucocytes as an aid to differential diagnosis between various affections acute and chronic. Although certain extravagant assertions have no doubt been made, still evidence is quickly accumulating which is placing the examination of the leucocytes of the circulating blood in an important position in clinical diagnosis.

To enter fully into the discussion of these diagnostic points would be beyond the limits of a thesis such as this. It may not be out of place here however to make certain general statements which appear to me to be of some importance in this connection.

Ehrlich has insisted upon the circumstance that the cells in the local exudation correspond with the cells which are found increased in the circulating blood, and I have pointed out that no acute inflammatory exudation of any size can take place without evidence thereof being present in the circulating blood.

What then are the signs of an acute inflammatory process (with the exudation of polynuclear leucocytes) present in the blood of the general circulation ?

1. The first sign to appear is the absolute

- diminution

diminution in number or total disappearance of the eosinophilic cells.

For instance I have seen cases where minute foci of suppination were present, e.g. in surgical kidney, where the leucocyte count was not raised, and the only deviation in the blood from the normal was the absence of eosinophiles.

Note that in scarlet fever and frequently also in acute rheumatism the eosinophilic cells do not disappear from the blood.

2. The second sign of value is relative increase of the large mononucleated cells, as compared with the lymphocytes, with or without increase in the total number of leucocytes per c.m.m.

This phenomenon is seen especially in cases of leucocytosis of moderate intensity, also sometimes at the commencement and more frequently towards the close of a typical neutrophile leucocytosis. It is also seen if any quick change takes place in the total number of leucocytes per c.m/m.

3. The third sign - that of an intense leucocytosis - is great relative increase of the polynuclear cells over the other forms, with increase in the total number of white cells per c.m/m.

(Note .- A leucocytosis may be of relatively low count and of transient duration but be very intense while it lasts and show a very high relative percentage of polynuclear cells.

Again the leucocyte count may be very high but

-the

the chemotactic force though present in large amount may be of moderate intensity and the leucocytosis presents as its most striking feature increase of the large mononuclear cells. All combinations of these factors will naturally suggest themselves.)

A practical point of importance to be deduced from the above statements is this :- a normal count of leucocytes, with the lymphocytes and the large mononuclear cells in their proper ratios and the presence of the eosinophiles negatives the occurrence of an acute inflammatory process. To cite a case : In a female patient with a temperature of 100 - 101 F. there was present a swelling deep in left lumbar region of the abdomen, tender to pressure. The surgical diagnosis was an acute abscess. I examined the blood while the temperature was still high and found that the leucocytes numbered 6,500 per c.m/m.; the polynuclear cells made up 65%, the large mononuclear group 7%, the lymphocytes 24%, and the eosinophiles 4% of those . In other words the blood examination was directly opposed to abscess formation. At the operation there was found an extravasation of blood behind the peritoneum.

Not only however is the examination of the haemic leucocytes an aid to diagnosis but it may furnish us with valuable suggestions regarding pathology of various affections. Two examples will suffice to make my meaning clear.

(1) In asthma there is present a great increase of eosinophiles in the blood and the expectoration is - chiefly

chiefly made up of these cells. In acute urticaria a large augmentation in the eosinophiles in the blood has been noted. One of the views regarding the pathology of asthma is that it is an urticaria of the bronchial mucous membrane.

(2) In rickets Rieder and others have noted a great diminution in the polynuclear leucocytes. Ehrlich, Muir and others, believe that those cells are derived from the finely granular cells of the bone marrow.

With these more or less disconnected remarks I bring this thesis to a close, confident that, although during the past year or two much light has been thrown upon the subject matter of my dissertation, we are but standing on the brink of fresh discovery.

F I N I S.